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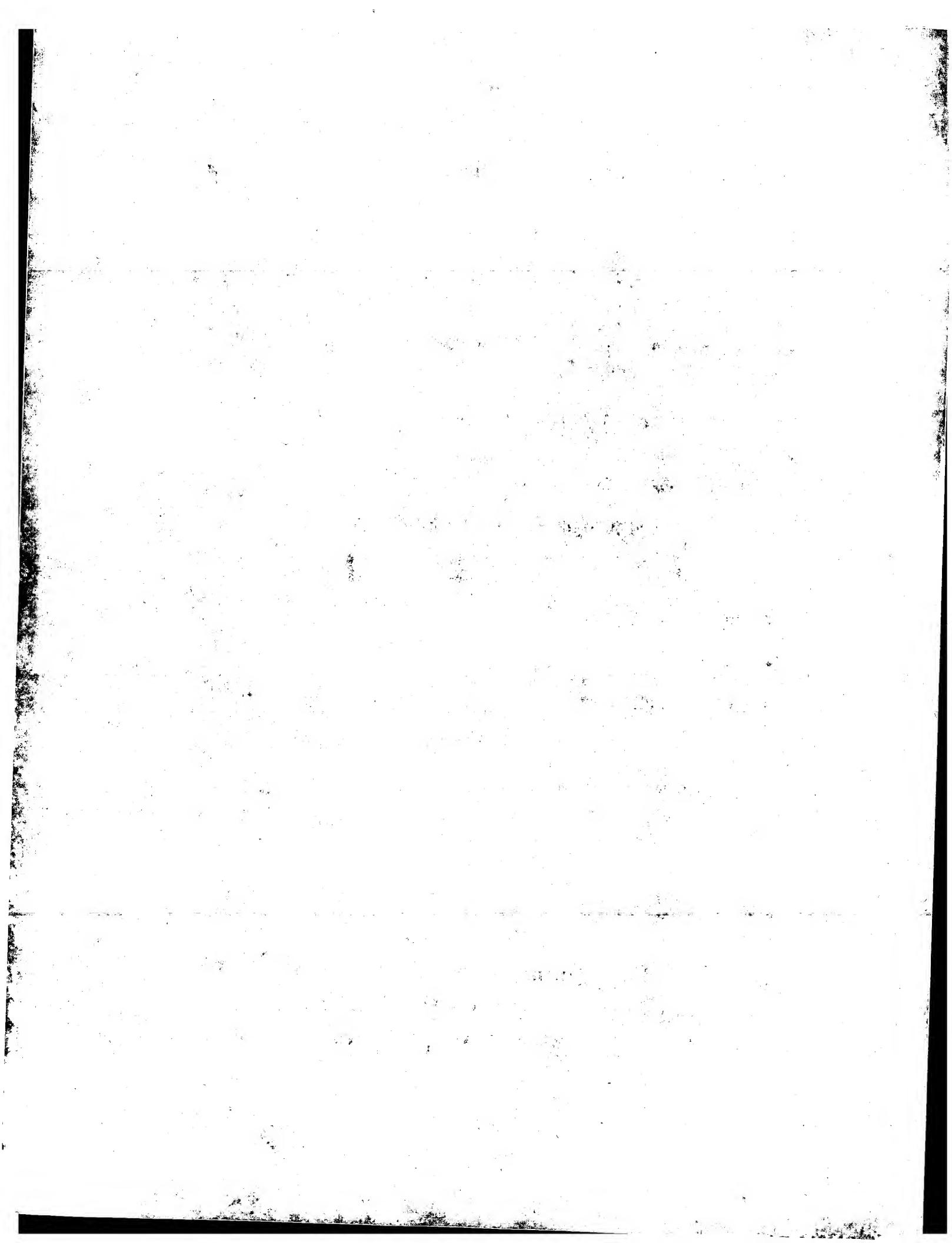
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

* * * * *

Applicants: Christine ANDREONI, et al.
Serial No.: 09/647,309
Filed : January 3, 2001
Title : Use of active P40 conjugates for nasal delivery

* * * * *

HON. COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

**CLAIM TO PRIORITY AND FILING OF PRIORITY DOCUMENT
UNDER 37 CFR § 1.55 AND 35 USC § 119**

Sir:

Herewith please find a copy of French priority application Serial No. 9803814 filed March 27, 1998, and certified translation thereof into English, the right of priority of which was claimed upon filing of the above-identified application, and which claim is hereby repeated.

Respectfully submitted,

THE FIRM OF HUESCHEN & SAGE

By:

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Dated: March 8, 2004.

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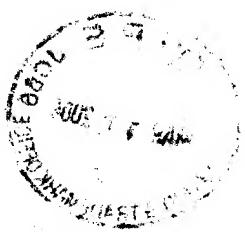
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HUESCHEN AND SAGE

Dated: March 8, 2004





IN THE MATTER OF an Application
for a French Patent
in the name of
PIERRE FABRE MEDICAMENT
filed under **No. 98 03 814** , and
IN THE MATTER OF an Application
for an American Patent.

I, Michel Pernelle,
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do solemnly and sincerely declare that I am conversant with the French and English languages
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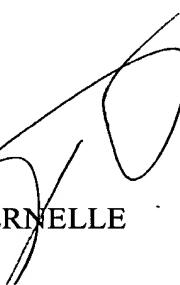
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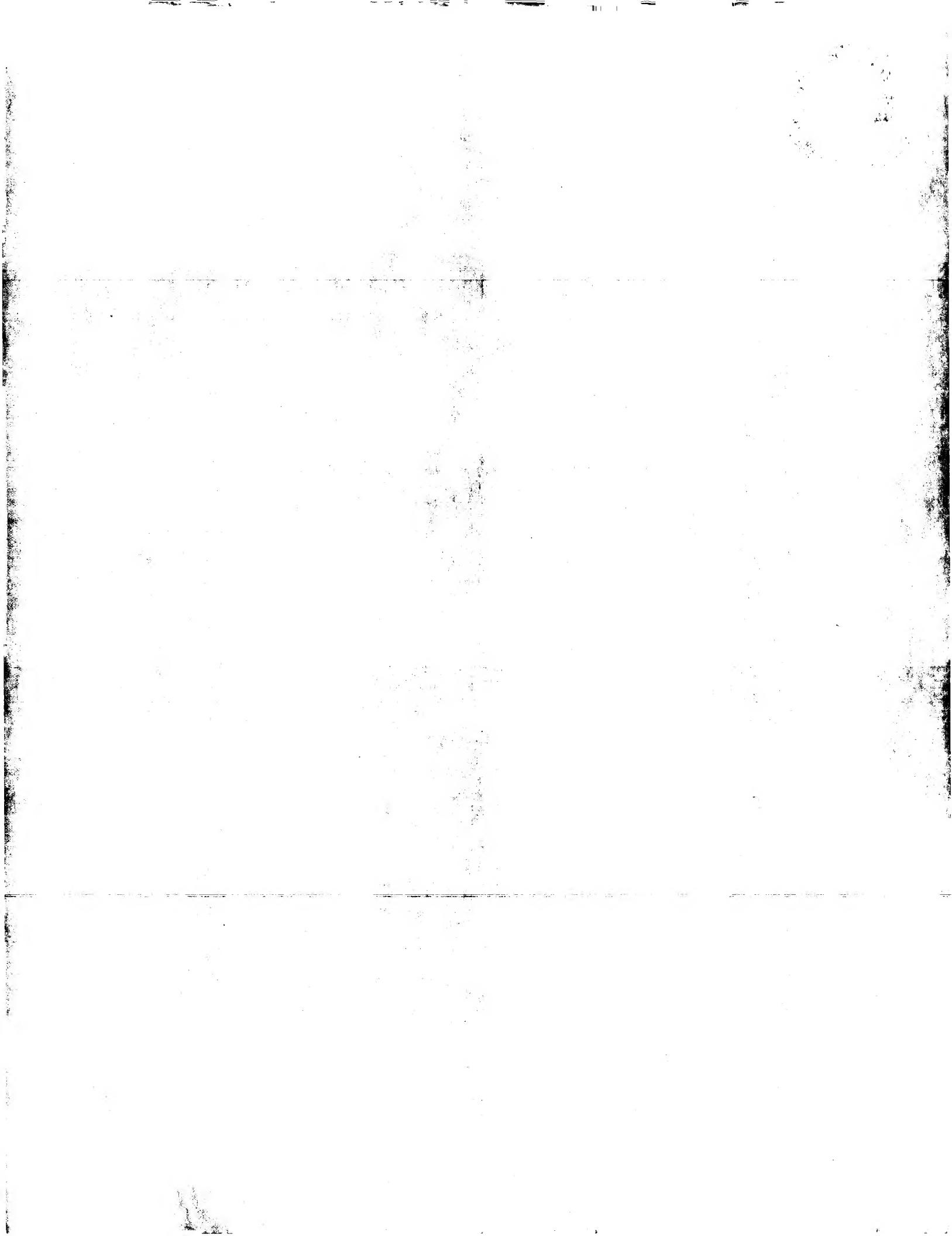
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DESIGNATION OF THE INVENTOR
(if the applicant is not the inventor or the sole inventor)

NATIONAL REGISTRATION NO.

98/03,814

TITLE OF THE INVENTION: **Use of active P40 conjugates for nasal delivery**

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Date and signature(s) of the applicant(s) or of the representative

27 March 1998

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DOCUMENT CONTAINING AMENDMENTS

* A change made in the wording of the original claims, unless the change derives from the provisions of Article R.612-36 of the Intellectual Property Code, is indicated by the reference "R.M." (amended claims).

The present invention relates to the production of immunizing preparations which are effective in nasal administration. It thus relates to the use of carrier 5 proteins which can improve the immune response to a hapten when the hapten/carrier protein conjugate is administered nasally.

The use of vaccine for oral or nasal delivery is thought to have a great influence on the eradication 10 of pathogenic microorganisms. Specifically, any modification of a vaccine which allows it to be used with greater flexibility (heat-stability, distribution without syringes, etc.), would result in a more effective and more widely used vaccination. On the 15 other hand, immunization via the mucous membrane pathways makes it possible to induce a local immunity which constitutes the first barrier against invasion by a microorganism.

Currently, the oral vaccines which are on the 20 market only concern attenuated or recombined live vectors:

- tetravalent oral vaccine against polio,
- oral vaccine against typhoid fever.

Approaches for nasal or oral vaccination are 25 already described in the literature.

Tests have thus been carried out on mucosal administrations of PspA, which corresponds to the surface protein A of Pneumococcus (Briles D.E., patent EP 0,682,950), on hemagglutinin filaments (Capron A., patent FR 2,718,750; Kimura A., patent EP 0,471,177; 30 Shahin R.D., US patent 7532327), on a fragment of the tetanus toxin (Dougan G., patent WO 93/21950) and on cholera toxin B (CTB).

A protein of the external membrane of *Neisseria meningitidis* is used, mixed with the hapten as an adjuvant for a nasal immunization (Van de Verg L.L., Infection and immunity, 1996, 64: 5263-5268).

Unexpectedly, the Applicant has now found that a membrane protein originating from another bacterium

makes it possible, when it is administered nasally together with an antigen, to induce an immune response of satisfactory strength and quality for the production of a vaccine.

5 For this reason, the subject of the present invention is the use of at least one fragment of an enterobacterium membrane protein OmpA for preparing a pharmaceutical composition intended to be administered nasally, to improve the immunity of a mammal with
10 respect to an antigen or to a hapten.

In the present invention, the term "OmpA" is intended to refer to the type A proteins of the external membrane (OmpA for Outer membrane protein A).

A subject of the invention is also the use of
15 at least one fragment of a membrane protein of Klebsiella for preparing a pharmaceutical composition intended to be administered nasally, to improve the immunity of a mammal with respect to an antigen or to a hapten.

20 Preferably, the membrane protein is an OmpA protein of *Klebsiella pneumoniae*.

Advantageously, said fragment of the enterobacterium membrane protein OmpA or of the Klebsiella membrane protein according to the invention
25 is obtained by recombinant process.

Very advantageously, said membrane protein or its fragment, obtained by recombinant process, is, after extraction, renatured in the presence of detergent chosen from Zwittergent 3-14, Zwittergent
30 3-12 and octylglycopyranoside, preferably in the presence of Zwittergent 3-14 at a concentration of between 0.05% and 2% (w/v), very preferably at a concentration close to 0.1%.

Application WO 96/14415 has shown that the
35 major membrane protein of *Klebsiella pneumoniae*, which is the OmpA named P40, coupled to peptide subunit antigens is very immunogenic via the systemic route. The recombinant P40 protein, expressed in E.Coli in the form of inclusion bodies, is named rP40.

In the context of the present invention, a particularly suitable protein comprises the sequence SEQ ID No 1.

The Applicant has demonstrated that an anti-P40 antibody response is found in all adults, the *Enterobacterium Klebsiella pneumoniae* being a very widespread pathogen. This sensitization favors an increase in the antibody response directed against an antigen or a hapten which is administered while coupled 10 to the carrier protein P40. The administration is carried out nasally in the absence of adjuvant.

Said antigen or hapten according to the invention can be chosen from the group comprising proteins, peptides, polysaccharides, oligosaccharides 15 and nucleic acids. Advantageously, it is of bacterial or viral origin.

The present invention is thus suitable for preparing vaccine directed against any microorganism responsible for pathologies of the airways, such as for 20 example microorganisms chosen from RSV, parainfluenzae virus (PIV), influenza virus, hantavirus, streptococci, pneumococci and meningococci.

The antigen or hapten according to the invention will comprise at least one fragment of said 25 microorganism, such as a protein fragment, which persons skilled in the art will know how to determine for its capacity to confer the desired immunity, by standard techniques such as those described in the examples below.

30 In particular, the present invention is suitable for preparing vaccine directed against RSV (or respiratory syncytial virus), in particular human or bovine RSV. In this case, the antigen or hapten according to the invention comprises at least one 35 protein fragment of the virus RSV, and in particular at least one fragment of the protein G of the RSV.

The sequences of such fragments have in particular been described in application WO 95/27787.

Preferably, said protein fragments of the virus RSV are chosen from the fragments having the sequences SEQ ID No 2 to SEQ ID No 73 as amino acid sequences.

Sequences which are suitable for preparing a 5 vaccine according to the invention are the sequences SEQ ID No 2 to SEQ ID No 73.

The chemical conjugates derived from the coupling of peptides to at least one fragment of a membrane protein of Klebsiella, such as rP40, give good 10 results, and an evaluation of the immune response shows very strong antibody responses against these peptides after presensitization with *Klebsiella pneumoniae*.

Advantageously, the protein fragment originating from enterobacteria membrane protein OmpA 15 or from membrane protein of Klebsiella is covalently coupled to the antigen or hapten, such as a protein fragment of the RSV.

The invention also comprises the use of at least one fragment of an enterobacteria membrane 20 protein OmpA or of a membrane protein of Klebsiella according to the invention, characterized in that said fragment is covalently coupled to said antigen or hapten.

According to the invention, it is possible to 25 introduce one or more bonding elements, in particular amino acids, to facilitate the coupling reactions between the fragment of membrane protein and the antigen or hapten.

The covalent coupling of the antigen or hapten 30 according to the invention can be carried out at the N- or C-terminal end of the fragment of the membrane protein according to the invention. The bifunctional reagents which allow this coupling can be determined as a function of the end of the fragment of the membrane 35 protein which is chosen to perform the coupling, and of the nature of the antigen or hapten to be coupled. These coupling techniques are well known to persons skilled in the art.

The conjugates derived from the coupling of peptides to at least one fragment of an enterobacteria membrane protein OmpA or of a membrane protein of Klebsiella can be prepared by genetic recombination.

5 The hybrid protein (conjugate) can in fact be produced by recombinant DNA techniques, by insertion or addition of a sequence encoding the antigenic or hapten peptide(s) into or to the DNA sequence encoding the fragment of membrane protein. These techniques for 10 preparing hybrid protein by genetic recombination are well known to persons skilled in the art (cf. for example S.C. MAKRIDES, 1996, *Microbiologicals Reviews*, 60, 3, 512-538) and will not be developed in the present description.

15 Thus, the invention also comprises the use, according to the invention, characterized in that the hybrid protein, obtained after coupling between the fragment of a membrane protein and the antigen or hapten, protein in nature, is prepared by genetic 20 recombination.

The Applicant has also shown that, in the absence of sensitization to *Klebsiella pneumoniae*, the nasal administration of a hapten coupled to at least one fragment of a membrane protein, such as the rP40 25 protein, in the absence of adjuvant, induced an anti-hapten antibody response.

The invention relates to the use, according to the invention, characterized in that the pharmaceutical composition contains a fragment of a membrane protein 30 coupled to an antigen or hapten according to the invention, or a transformed host cell which is capable of expressing a hybrid recombinant protein containing a fragment of membrane protein coupled to the antigen or hapten according to the invention, in particular in the 35 absence of adjuvant. Among the transformed host cells which are capable of expressing said hybrid protein, gram-negative bacteria such as *Klebsiella pneumoniae*, *Escherichia coli* type K12 currently used in fermentation, or *E. coli* transformed with an expression

vector plasmid containing a strong promoter such as the operon of the tryptophan promoter (trp) are preferred. Also preferred are gram-positive bacteria such as the nonpathogenic staphylococci, *S. carnosus* and 5 *S. xylosus*, since these bacteria do not produce any LPS (lipopolysaccharides) at the membrane surface. These staphylococci can be transfected with expression vectors containing promoters such as trp, or the secretion signal of lipase or even the secretion signal 10 of protein A, or alternatively the signal of the promoter of OmpA of *Klebsiella pneumoniae*.

Finally, the invention relates to a method for preparing a protein or one of its fragments by the recombinant pathway, characterized in that the protein 15 or its fragment is, after extraction, renatured in the presence of a solution containing a detergent chosen from Zwittergent 3-14, Zwittergent 3-12 and octylglucopyranoside, and in that said recombinant protein is not interferon β .

20 Preferably, said protein is an enterobacterium membrane protein, in particular of OmpA type. Very preferably, said protein is an OmpA of *Klebsiella pneumoniae*.

In the method according to the invention, the 25 Zwittergent 3-14 will be preferably at a concentration of between 0.05% and 2%, more preferably close to 0.1%.

The following examples are intended to illustrate the invention without in any way limiting the scope thereof.

30 In these examples, reference will be made to the following figures:

Figure 1: Analysis by SDS-PAGE electrophoresis of the rP40 protein after purification.

A: detection with Coomassie blue

35

- lane 1: batch 1, 2 μ g
- lane 2: batch 1, 10 μ g
- lane 3: batch 2, 2 μ g
- lane 4: batch 2, 10 μ g
- lane 5: batch 3, 2 μ g

- lane 6: batch 3, 10 µg

B: immunoblot and detection with the aid of an anti-rP40 rabbit polyclonal serum

- std: molecular mass standard

5 - lane 1: denatured rP40, 100 ng
- lane 2: native rP40, 100 ng.

Figure 2: Division of the patients according to the O.D. (Optical Density) corresponding to the anti-rP40 antibodies, measured by ELISA.

10 **Figure 3:** Anti-G1' antibody response.

Figure 4: Anti-rP40 antibody response.

Figure 5: Anti-G1' IgA-type antibody response.

Figure 6: Isotyping of the anti-G1' immunoglobulins obtained in secondary response.

15 **Figure 7:** Isotyping of the anti-G1' immunoglobulins obtained in tertiary response.

Figure 8: Anti-G1' total IgG-type serum antibody response.

20 **Figure 9:** Isotyping of the serum anti-G1' immunoglobulins after three immunizations.

Figure 10: Isotyping of the anti-G1' immunoglobulins from broncho-alveolar washes after three immunizations.

Example 1: Cloning of rP40

25 **Cloning of the rP40 gene:**

The gene encoding rP40 was obtained by amplification by PCR (Polymerase Chain Reaction) from the chromosomal DNA of the *Klebsiella pneumoniae* IP 1145 strain (described in patent WO 96/14415). After 30 identification by DNA sequencing, the fragment corresponding to rP40 is cloned into diverse expression vectors, in particular the one under the control of the *trp* operon promoter, upstream of 9 amino acids of the leader peptide (MKAIFVLNA). The peptide sequence of 35 rP40 is represented in the sequence listing by the sequence SEQ ID No 1. In various *E.coli* K12 strains, the rP40 protein is produced in the form of inclusion bodies with a considerable yield (> 10%, g proteins/g of biosolids).

Fermentation of rP40 fusion proteins:

E. coli K12 transformed with the plasmid pvaLP40 is inoculated in an Erlenmeyer flask containing 250 ml of TSB (Tryptic Soy Broth, Difco) medium 5 containing ampicillin (100 µg/ml, Sigma) and tetracycline (8 µg/ml, Sigma). This is incubated for 16 hours at T° = 37°C with stirring. 200 ml of this culture are inoculated in a fermenter (CHEMAP CF3000, ALFA LAVAL) containing 2 liters of culture medium. The 10 medium contains (g/l): glycerol, 5; ammonium sulfate, 2.6; potassium dihydrogen phosphate, 3; dipotassium hydrogen phosphate, 2; sodium citrate, 0.5; yeast extract, 1; ampicillin, 0.1; tetracycline 0.008; thiamine, 0.07; magnesium sulfate, 1 and 1 ml/l of 15 trace element solution and 0.65 ml/l of vitamin solution. The parameters which are controlled during the fermentation are: pH, stirring, temperature, degree of oxygenation, supply of combined sources (glycerol or glucose). The pH is regulated at 7.0. The temperature 20 is fixed at 37°C. The growth is controlled by supplying with glycerol (87%) at a constant flow rate (12 ml/h) so as to maintain the dissolved oxygen tension signal at 30%. When the turbidity of the culture (measured at 25 580 nm) reaches the value of 80 (after approximately 24 hours of culture), protein production is induced by adding indole acrylic acid (IAA) to a final concentration of 25 mg/l. Approximately 4 hours after induction, the cells are harvested by centrifugation. The amount of biomass obtained is approximately 200 g, 30 expressed as wet biomass.

Example 2: Extraction and purification of rP40

Materials and methods

Extraction of rP40

After centrifugation of the culture medium 35 (4000 rpm, 10 min, 4°C), the cells are resuspended in a 25 mM Tris-HCl buffer, pH 8.5. A treatment with lysozyme (0.5 g/l, 1 hour/room temperature/gentle stirring) allows the release of the inclusion bodies.

The pellet of inclusion bodies obtained by centrifugation (25 min at 10,000 g at 4°C) is taken up in a 25 mM Tris-HCl buffer, pH 8.5, containing 5 mM MgCl₂, and then centrifuged (15 min at 10,000 g).

5 The denaturation of the protein is obtained by incubating the inclusion bodies at 37°C for 2 hours in a 25 mM Tris-HCl buffer, pH 8.5, containing 7 M urea (denaturing agent) and 10 mM dithiothreitol (reduction of disulfide bridges). A centrifugation (15 min at 10,000 g) makes it possible to remove the insoluble portion of the inclusion bodies.

10 After dilution with 13 volumes of a 25 mM Tris-HCl buffer, pH 8.5, containing NaCl (8.76 g/l) and Zwittergent 3-14 (0.1%, w/v), the mixture is left to 15 stand overnight at room temperature with stirring, in contact with the air (renaturation of the protein by dilution and reoxidation of the disulfide bridges).

Purification of the rP40 protein

Anion exchange chromatography step.

20 After another centrifugation, the sample is dialyzed against a 25 mM Tris-HCl buffer, pH 8.5, containing 0.1% Zwittergent 3-14 (100 volumes of buffer) overnight at 4°C.

25 The dialyzate is loaded onto a column containing a support of strong anion exchanger type (Biorad Macro Prep High Q gel), which is equilibrated in the buffer described above at a linear flow rate of 15 cm/h. The proteins are detected at 280 nm. The rP40 protein is eluted, with a linear flow rate of 60 cm/h 30 for an NaCl concentration of 0.6 M, in the 25 mM Tris/HCl buffer, pH 8.5; 0.1% Zwittergent 3-14.

Cation exchange chromatography step.

35 The fractions containing the rP40 protein are pooled and concentrated by ultrafiltration with the aid of an Amicon cell system with stirring used with a Diaflo membrane of type YM10 (cutoff threshold 10 kDa) for volumes of about 100 ml, or with the aid of a Millipore Minitan tangential flow filtration system used with membrane plates having a cutoff threshold of

10 kDa, for larger volumes. The fraction thus concentrated is dialyzed overnight at 4°C against a 20 mM citrate buffer, pH 3.0, containing 0.1% of Zwittergent 3-14.

5 The dialysate is loaded onto a column containing a support of strong cation exchanger type (Biorad Macro Prep High S gel), which is equilibrated in the 20 mM citrate buffer, pH 3.0, containing 0.1% of Zwittergent 3-14. The rP40 protein is eluted (rate 10 61 cm/h) for a 0.7 M NaCl concentration. The fractions containing the rP40 are pooled and concentrated as described above.

Results

15 Starting from a 1 liter culture, one denaturation/renaturation cycle makes it possible to obtain 300 mg of protein (estimation by assay according to the Lowry method). 75 mg of rP40 are purified after the two chromatographic steps.

20 As above, the rP40 protein is concentrated after purification in order to attain a final concentration of between 5 and 10 mg/ml. The electrophoretic profiles show a degree of purity of about 95% (Figure 1A). After immunoblot, the protein is specifically recognized by an anti-natural P40 25 monoclonal antibody obtained in mice (Figure 1B).

The condition of the protein is monitored by SDS-PAGE. Depending on its form, denatured or native, the P40 protein extracted from the membrane of *Klebsiella pneumoniae* has a characteristic 30 electrophoretic behavior (migration). The native form (β -sheet structure) in fact has a lower molecular mass than the denatured form (α -helix structure) under the action of a denaturing agent, such as urea or guanidine hydrochloride, or with heating to 100°C in the presence 35 of SDS (Figure 1B). The rP40 protein is not correctly renatured at the end of renaturation, regardless of whether this is carried out in the presence or absence of 0.1% (w/v) Zwittergent 3-14. Conversely, total renaturation is obtained after dialysis against a 25 mM

Tris/HCl buffer, pH 8.5, containing 0.1% (w/v) Zwittergent 3-14. However, it should be noted that this renaturation is only obtained when the dilution step and the treatment at room temperature are themselves 5 carried out in the presence of Zwittergent 3-14 (negative results in the absence of detergent).

Example 3: Coupling of the G1' peptide to rP40

Materials and methods

10 The G1' peptide is a synthetic peptide of 15 amino acids, the sequence of which is as follows:

N₁SIDSNNPTOWAISKC₁₅C

15 Without the Cys (cysteine) residue added in the C-terminal position, this peptide (portion 1-14) corresponds to portion 174-187 of the protein G of the respiratory syncytial virus, and has, with respect to the native peptide, two major modifications which are:

- the replacement of the Cys residue at position 13 with a Ser (serine) residue,
- the replacement at positions 3 and 9 of the Cys residues, which form a disulfide bridge, with, respectively, Asp (aspartic acid) and Orn (ornithine) residues which form a lactam-type bridge.

20 These modifications are introduced for the purpose of removing the Cys residues of the native peptide in order to be able to carry out a one-to-one coupling of the latter to the protein via the Cys residue introduced in the C-terminal position, while at the same time maintaining the structure of the peptide with the aid of the introduction of a lactam bridge.

30 The coupling of the peptide to the protein is carried out using the BHA or bromo-N-hydroxysuccinimide acetate reagent (Svenson et al., 1990, Proc. Natl. Acad. Sci. USA 87, 1347, Bernatowicz and Matsueda, 1986, Anal. Biochem. 155, 95). This heterobifunctional 35 reagent allows activation of the Lys (lysine) residues of the protein by bromoacetylation, and then coupling of the peptide via the free thiol group carried by the Cys residue.

Firstly, the rP40 protein is activated with the BHA. The rP40 is dialyzed against a 0.1 M phosphate buffer, pH 7, containing 0.1% Zwittergent 3-14, for 24 hours at +4°C. After dialysis, the concentration is 5 adjusted to 5 mg/ml with the aid of the same buffer, before adding BHA in a proportion of 1.2 mg (50 µl)/mg of rP40.

The whole is placed in the dark for one hour with stirring and at room temperature.

10 The activated rP40 is then desalified by gel filtration chromatography (elution with the abovementioned buffer). The fractions containing the bromoacetylated protein are pooled.

15 For the coupling, the peptide (10 mg/ml in 0.1 M phosphate buffer, pH 7, containing 0.1% Zwittergent 3-14) is added to the activated protein in a proportion of 0.4 mg/mg of protein. After saturation under a nitrogen stream, the tube is again placed in the dark for 2 hours with stirring and at room 20 temperature.

The unbound peptide can be removed with the aid of a dialysis step or of molecular sieve chromatography.

Results

25 The conjugate obtained is characterized by protein assay (BCA or LOWRY method) and by SDS-PAGE electrophoresis. The degree of coupling of the peptide to the protein is estimated by carboxymethylcysteine residue assay: the assaying of the amino acids released 30 by hydrolysis (6N HCl) is performed by HPLC after derivatization with the aid of PITC (Pico-Tag method, Waters).

The degree of coupling determined by this method is approximately 10 G1' peptides/mole of rP40.

35 Example 4: Natural immunity in adults

Human sera derived from a clinical study are analyzed by ELISA assay in order to determine the presence of anti-P40 antibodies.

The results are represented in Figure 2.

Among 113 sera tested after 400-fold dilution, 110 sera give a colorimetric signal revealing the anti-P40 IgGs. There are circulating anti-P40 antibodies in all the patients, with levels which are more or less 5 high depending on the patient under consideration.

Example 5: Anti-G1' antibody response after sensitizations and frequent immunizations

BALB/c mice were or were not sensitized twice with a *Klebsiella pneumoniae* I145 strain, in order to 10 reproduce the seropositivity found in humans. The mice are subsequently immunized nasally in the absence of adjuvant 7 days after the sensitization. This 15 immunization is carried out with a small amount of antigen, the mice receiving 10 µg of G1' equivalent coupled to rP40. The mice receive a booster 10 and 20 days after the first immunization. A retro-orbital 20 sinus puncture is performed on the mice 9 days after the first immunization and 10 days after each booster (secondary and tertiary responses). The serum anti-G1' 25 (Figure 3) and anti-carrier (Figure 4) antibodies are assayed by the ELISA method.

5.1 Assaying of anti-G1' serum IgGs

The results are represented in Figure 3.

In the primary response, the mice presensitized 25 with *Klebsiella pneumoniae* and immunized with rP40-G1' are the only ones to produce anti-G1' antibodies.

The level of anti-G1' antibodies found in the mice presensitized with *Klebsiella pneumoniae* and immunized with rP40-G1' is increased after a second 30 immunization. In the absence of presensitization, a second immunization in the presence of the rP40-G1' conjugates induces an anti-G1' antibody response.

After three immunizations, the anti-G1' antibody response is increased in the presensitized and 35 non-presensitized mice.

5.2 Assaying of anti-rP40 serum IgGs

The results are represented in Figure 4.

The anti-P40 antibody response shows that the mice were sensitized to *Klebsiella pneumoniae* in

identical manner whatever the batch under consideration.

The immunization in the presence of rP40-G1' conjugates slightly increases the anti-rP40 antibody 5 response.

5.3 Assaying of anti-G1' serum IgAs

Secondly, we assayed the serum IgA-type anti-G1' antibody response: immunoglobulin characteristic of immunizations carried out via the mucous membrane 10 (nasal or oral) pathways.

The results are represented in Figure 5.

After a single immunization, IgAs are not detected. After two immunizations, anti-G1' IgAs are detected essentially in mice presensitized to 15 *Klebsiella pneumoniae* and immunized with rP40-G1'. This response is increased by the third immunization. In the absence of sensitization, anti-G1' IgAs are detected in mice after two immunizations with rP40-G1' conjugates. This level of IgA is increased by the third 20 immunization.

5.4 Isotyping of anti-G1' serum immunoglobulins

Two types of response can be observed, Th1 and Th2. These responses differ by the profile of cytokines produced and by their functions in the immune response. 25 IgG1s are characteristic of a response of type Th2, and IgG2as are characteristic of a Th1 response.

A mixed Th1 and Th2 response profile is found only in the mice immunized with the rP40-G1' conjugates, whether or not they are presensitized with 30 *Klebsiella pneumoniae* (Figure 6).

After three immunizations (Figure 7), the profile remains mixed in the mice immunized with the rP40-G1' conjugates.

Example 6: Anti-G1' antibody response after 35 sensitizations and infrequent immunizations.

With respect to the above protocol, the first immunization is separated from the final sensitization by a period of 3 weeks instead of one week. The anti-G1' antibodies are assayed in the sera, and, in the

tertiary response, in broncho-alveolar washes, by the ELISA method.

6.1 Assaying of anti-G1' serum IgGs

As seen in Figure 8, 7 days after the first 5 immunization, anti-G1' serum antibodies of type total IgG are detected in the mice presensitized to *Klebsiella pneumoniae* and immunized in the presence of the rP40-G1' conjugates. This antibody response is increased by the two other immunizations.

10 6.2 Isotyping of serum immunoglobulins

The results are represented in Figure 9.

In this case, we also observe a mixed response, we obtain in fact the same titer for IgG1 as for IgG2a (Figure 9). In addition, a high level of IgA is found 15 in the mice presensitized to *Klebsiella pneumoniae* and immunized three weeks later in the presence of the rP40-G1' conjugates.

6.3 Isotyping of immunoglobulins from broncho-alveolar washes

20 In the broncho-alveolar washes, the 4 types of immunoglobulin are found only in the mice sensitized to *Klebsiella pneumoniae* and immunized 3 times in the presence of the rP40-G1' conjugates (Figure 10).

SEQUENCE LISTING

Information for SEQ ID NO: 1 rP40

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 344 amino acids, 1032 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

1 12
N - Met Lys Ala Ile Phe Val Leu Asn Ala Ala Pro Lys
5' - ATG AAA GCA ATT TTC GTC CTG AAT GCG GCT CGG AAA
30
Asp Asn Thr Trp Tyr Ala Gly Gly Lys Leu Gly Trp Ser Gln Tyr His Asp Thr
GAT AAC ACC TGG TAT GCA CGT CGT AAA CTG CGT TGG TCC CAG TAT CAC GAC ACC
48
Gly Phe Tyr Gly Asn Gly Phe Gln Asn Asn Gly Pro Thr Arg Asn Asp Gln
GGT TTC TAC GGT AAC GGT TTC CAG AAC AAC GGT CGG ACC CGT AAC GAT CAG
66
Leu Gly Ala Gly Ala Phe Gly Gly Tyr Gln Val Asn Pro Tyr Leu Gly Phe Glu
CTT CGT GCT GGT GCG TTC GGT TAC CAG GTC AAC CGG TAC CTC CGT TTC GAA
84
Met Gly Tyr Asp Trp Leu Gly Arg Met Ala Tyr Lys Gly Ser Val Asp Asn Gly
ATG CGT TAT GAC TGG CTG GGC CGT ATG GCA TAT AAA GGC AGC GTT GAC AAC CGT
102
Ala Phe Lys Ala Gln Gly Val Gln Leu Thr Ala Lys Leu Gly Tyr Pro Ile Thr
GCT TTC AAA GCT CAG GGC GTT CAG CTG AOC CCT AAA CTG GGT TAC CGG ATC ACT
120
Asp Asp Leu Asp Ile Tyr Thr Arg Leu Gly Gly Met Val Trp Arg Ala Asp Ser
GAC GAT CTG GAC ATC TAC ACC CGT CTG CGC CGC ATG GTT TGG CGC GCT GAC TCC
138
Lys Gly Asn Tyr Ala Ser Thr Gly Val Ser Arg Ser Glu His Asp Thr Gly Val
AAA CGC AAC TAC GCT TCT ACC GGC GTT TCC CGT AGC GAA CAC GAC ACT CGC GTT
156
Ser Pro Val Phe Ala Gly Gly Val Glu Trp Ala Val Thr Arg Asp Ile Ala Thr
TCC CCA GTC TTT GCT GGC GGC GTC GAG TGG CCT GTT ACT CGT GAC ATC GCT ACC
174
Arg Leu Glu Tyr Gln Trp Val Asn Asn Ile Gly Asp Ala Gly Thr Val Gly Thr
CGT CTG GAA TAC CAG TGG GTT AAC AAC ATC CGC GAC CGG GGC ACT GTG GGT ACC
192
Arg Pro Asp Asn Gly Met Leu Ser Leu Gly Val Ser Tyr Arg Phe Gly Gln Glu
CGT CCT GAT AAC CGC ATG CTG ACC CTG CGC GTT TCC TAC CGC TTC GGT CAG GAA
210
Asp Ala Ala Pro Val Val Ala Pro Ala Pro Ala Pro Glu Val Ala Thr
GAT GCT GCA CGG GTT GCT CGT CCT CGG CCT CGG GCT CGG GAA GTG GCT ACC
228
Lys His Phe Thr Leu Lys Ser Asp Val Leu Phe Asn Phe Asn Lys Ala Thr Leu
AAG CAC TTC ACC CTG AAG TCT GAC GTT CTG AAC TTC AAC AAA GCT ACC CTG
246
Lys Pro Glu Gly Gln Gln Ala Leu Asp Gln Leu Tyr Thr Gln Leu Ser Asn Met
AAA CGG GAA GGT CAG CAG GCT CTG GAT CAG CTG TAC ACT CGG CTG AGC AAC ATG
264
Asp Pro Lys Asp Gly Ser Ala Val Val Leu Gly Tyr Thr Asp Arg Ile Gly Ser
GAT CGG AAA GAC CGT TCC GCT GTT CTG CGC TAC ACC GAC CGC ATC GGT TCC

282
Glu Ala Tyr Asn Gln Gln Leu Ser Glu Lys Arg Ala Gln Ser Val Val Asp Tyr
GAA CCT TAC AAC CAG CAG CTG TCT GAG AAA CGT GCT CAG TCC GTC GTT GAC TAC
300
Leu Val Ala Lys Gly Ile Pro Ala Gly Lys Ile Ser Ala Arg Gly Met Gly Glu
CTG GTT GCT AAA GGC ATC CGG GCT GGC AAA ATC TCC GCT CGC GGC ATG GGT GAA
318
Ser Asn Pro Val Thr Gly Asn Thr Cys Asp Asn Val Lys Ala Arg Ala Ala Leu
TCC AAC CGG GTT ACT GGC AAC ACC TGT GAC AAC GTG AAA GCT CGC GCT CGC CTG
336
Ile Asp Cys Leu Ala Pro Asp Arg Arg Val Glu Ile Glu Val Lys Gly Tyr Lys
ATC GAT TGC CTG CCT CGG GAT CGT GTC GAA GAG ATC GAA GTT AAA GGC TAC AAA
344
Glu Val Val Thr Gln Pro Gln Ala
GAA GTT GTC ACT CAG CCT CGG GCT

Information for SEQ ID NO: 2 G2A

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 101 amino acids, 303 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

130
N - Thr Val Lys Thr Lys Asn Thr Thr Thr Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys
5' - ACC GTG AAA ACC AAA AAC ACC ACC ACC CAG ACC CAG CGG AGC AAA CGG ACC ACC ACC AAA
150
Gln Arg Gln Asn Lys Pro Pro Asn Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe
CAG CGT CGG AAC AAA CGG CGG AAC AAA CGG AAC AAC GAT TTC CAT TTC GAA GTG TTC AAC TTC
171 173 176 182 186
Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn
GTG CGG TGC ACC ATC TCC AGC AAC AAC CGG ACC TCC TGG CGG ATC TCC AAA CGT ATC CGG AAC
192
Lys Lys Pro Gly Lys Lys Thr Thr Lys Pro Thr Lys Lys Pro Thr Phe Lys Thr Thr Lys
AAA AAA CGG CGC AAA AAA ACC AGC ACC AAA CGG ACC AAA AAA CGG ACC TTC AAA ACC ACC AAA
213 230
Lys Asp His Lys Pro Gln Thr Thr Lys Pro Lys Glu Val Pro Thr Thr Lys Pro - C
AAA GAT CAT AAA CGG CGG ACC ACC AAA CGG AAA GAA GTG CGG ACC ACC AAA CGG - 3'

Information for SEQ ID NO: 3 G2B

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 101 amino acids, 303 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

130
 N - Thr Ala Gln Thr Lys Gly Arg Ile Thr Thr Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys
 5' - ACC GCG CAG ACC AAA GGC CGT ATC ACC ACC AGC ACC CAG ACC AAC AAA CGG ACC ACC AAA
 150
 Ser Arg Ser Lys Asn Pro Pro Lys Pro Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe
 ACC CGT ACC AAA AAC CGG CGG AAA AAA CGG AAA GAT GAT TAC CAC TTC GAA GTG TTC AAC TTC

171	173	176	182	186																	
Val	Pro	Cys	Ser	Ile	Cys	Gly	Asn	Asn	Gln	Leu	Cys	Lys	Ser	Ile	Cys	Lys	Thr	Ile	Pro	Ser	
GIG	CCC	TCC	ACC	ATC	TCC	CCC	AAC	AAC	CAG	CTG	TCC	AAA	ACC	ATC	TCC	AAA	ACT	ATC	CGG	AGC	
192																					
Asn	Lys	Pro	Lys	Lys	Pro	Thr	Ile	Lys	Pro	Thr	Asn	Lys	Pro	Thr	Thr	Lys	Thr	Thr	Asn		
ATC	AAA	CGG	AAA	AAG	AAA	CGG	ACC	ATC	AAA	CGG	ACC	ATC	AAA	CGG	ACC	ACC	ACC	AAA	ACC	ACC	ATC
213																					
Lys	Arg	Asp	Pro	Lys	Thr	Pro	Ala	Lys	Met	Pro	Lys	Lys	Glu	Ile	Ile	Thr	Asn	- C	230		
AAA	CGT	GAT	CGG	AAA	ACC	CGG	GCG	AAA	ATG	CGG	AGC	AGG	GAA	ATC	ATC	ACC	ACC	AAA	- 3'		

Information for SEQ ID NO: 4 G2AδCys

SEQUENCE TYPE: amino acids and nucleotides
SEQUENCE LENGTH: 101 amino acids, 303 nucleotides
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: protein

130
 N - Thr Val Lys Thr Lys Asn Thr Thr Thr Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys
 5' - ACC GTG AAA ACC AAA AAC ACC ACG ACC ACC CAG ACC CAG CCG AGC AAA CCG ACC ACC AAA
 150
 Gln Arg Gln Asn Lys Pro Pro Asn Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe
 CAG CGT CAG AAC AAA CCG CCG AAC AAA CCG AAC GAC AAC GAT TTC CAT TIC GAA GTG TTC AAC TTC
 171 173 176 182 186
 Val Pro Ser Ser Ile Cys Ser Asn Asn Pro Thr Cys Trip Ala Ile Ser Lys Arg Ile Pro Asn
 GTG CCG AGC ACC ATC TGC AGC AAC AAC CCG ACC TCC TGG GCG ATC AGC AAA CGT ATC CCG AAC
 192
 Lys Lys Pro Gly Lys Lys Thr Thr Lys Pro Thr Lys Lys Pro Thr Phe Lys Thr Thr Lys
 AAA AAA CCG GCG AAA AAA ACC ACC AAC ACC AAA CCG ACC AAA AAA CCG ACC TIC AAA ACC ACC AAA
 213 230
 Lys Asp His Lys Pro Gln Thr Thr Lys Pro Lys Glu Val Pro Thr Thr Lys Pro - C
 AAA GAT CAT AAA CCG CAG ACC ACC AAA CCG AAA GAA GTG CCG ACC ACC AAA CCG - 3'

Information for SEQ ID NO: 5 G2BδCys

SEQUENCE TYPE: amino acids and nucleotides
SEQUENCE LENGTH: 101 amino acids, 303 nucleotides
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: protein

130

N - Thr Ala Gln Thr Lys Gly Arg Ile Thr Thr Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys
5' - ACC GCG CAG ACC AAA GGC CGT ATC ACC ACC ACC CGA ACC AAC AAA CGG ACC ACC AAA
150
Ser Arg Ser Lys Asn Pro Pro Lys Pro Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe
AGC CGT ACC AAA AAC CGG AAA AAA CGG AAA GAT GAT TAC CTC TTC GAA GIG TTC AAC TIC
171 173 176 182 186
Val Pro Ser Ser Ile Cys Gly Asn Asn Gln Leu Cys Lys Ser Ile Ser Lys Thr Ile Pro Ser
GIG CGC ACC ACC ATC TCC GGC AAC AAC CAG CTG TGC AAA AGC ATC AGC AAA ACC ATC CGG ACC

192

Asn Lys Pro Lys Lys Pro Thr Ile Lys Pro Thr Asn Lys Pro Thr Thr Lys Thr Asn
AAC AAA CGG AAA AAG AAA CGG ACC ATC AAA CGG ACC AAC AAA CGG ACC ACC AAA ACC AAC AAC
213 230
Lys Arg Asp Pro Lys Thr Pro Ala Lys Met Pro Lys Glu Ile Ile Thr Asn - C
AAA CGT GAT CGG AAA ACC CGG AAA ATG CGG AAG AAG GAA ATC ATC ACC AAC - 3'

Information for SEQ ID NO: 6 G1ACys

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 14 amino acids, 42 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

174 176 182 186 187
N - Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys - C
5' - AGC ATC TGC AGC AAC AAC CGG ACC TGC TGG CGG ATC TGC AAA - 3'

Information for SEQ ID NO: 7 G1BCys

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 14 amino acids, 42 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

174 176 182 186 187
N - Ser Ile Cys Gly Asn Asn Gln Leu Cys Lys Ser Ile Cys Lys - C
5' - AGC ATC TGC CGC AAC AAC CAG CTG TGC AAA AGC ATC TGC AAA - 3'

Information for SEQ ID NO: 8 G1A

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 14 amino acids, 42 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

174 176 182 186 187
N - Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile Ser Lys - C
5' - AGC ATC TGC AGC AAC AAC CCG ACC TGC TGG GCG ATC AGC AAA - 3'

Information for SEQ ID NO: 9 G1B

SEQUENCE TYPE: amino acids and nucleotides
SEQUENCE LENGTH: 14 amino acids, 42 nucleotides
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: peptide

174 176 182 186 187
N - Ser Ile Cys Gly Asn Asn Gln Leu Cys Lys Ser Ile Ser Lys - C
5' - AGC ATC TGC GGC AAC AAC CAG CTG TGC AAA AGC ATC AGC AAA - 3'

Information for SEQ ID NO: 10 G1'A

SEQUENCE TYPE: amino acids
SEQUENCE LENGTH: 14 amino acids
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: peptide

174 176 182 186 187
N - Ser Ile Asp Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys - C

Information for SEQ ID NO: 11 G1'B

SEQUENCE TYPE: amino acids
SEQUENCE LENGTH: 14 amino acids
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: peptide

174 176 182 186 187
N - Ser Ile Asp Gly Asn Asn Gln Leu Cys Lys Ser Ile Cys Lys - C

Information for SEQ ID NO: 12 G1'AδC

SEQUENCE TYPE: amino acids
SEQUENCE LENGTH: 14 amino acids
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: peptide

174 176 182 186 187
N - Ser Ile Asp Ser Asn Asn Pro Thr Orn Trp Ala Ile Ser Lys - C

Information for SEQ ID NO: 13 G1'BδC

SEQUENCE TYPE: amino acids

SEQUENCE LENGTH: 14 amino acids

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

174 176 182 186 187
N - Ser Ile Asp Gly Asn Asn Gln Leu Orn Lys Ser Ile Ser Lys - C

Information for SEQ ID NO: 14 G2AδCF

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 101 amino acids, 303 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

130
N - Thr Val Lys Thr Lys Asn Thr Thr Thr Thr Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys
5' - ACC GIG AAA ACC AAA AAC ACC ACC ACC CAG ACC CAG CGG AGC AAA CGG ACC ACC ACC ACC AAA

150 163 165 169 170
Gln Arg Gln Asn Lys Pro Pro Asn Lys Pro Asn Asn Asp Ser His Ser Glu Val Ser Asn Ser
CAG CGT CAG AAC AAA CGG CGG AAC AAA CGG AAC AAC GAT TCC CAT TCC GAA GTG TCC ANC TCC
171 173 176 182 186
Val Pro Ser Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile Ser Lys Arg Ile Pro Asn
GTG CGG AGC ACC ATC TCC ACC ANC AAC CGG ACC TGC TGG CGG ATC AGC AAA CGT ANC CGG AGC AAC
192
Lys Lys Pro Gly Lys Lys Thr Thr Lys Pro Thr Lys Pro Thr Phe Lys Thr Thr Lys
AAA AAA CGG CGC AAA ACC ACC ACC AAA CGG ACC AAA CGG AAA CGG ACC TTC AAA ACC ACC AAA
213 230
Lys Asp His Lys Pro Gln Thr Thr Lys Pro Lys Glu Val Pro Thr Thr Lys Pro - C
AAA GAT CAT AAA CGG CAG ACC ACC AAA CGG AAA GAA GTG CGG ACC ACC AAA CGG - 3'

Information for SEQ ID NO: 15 G4A

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 17 amino acids, 42 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

171 173 176 182 186 187
N - Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys - C
5' - GTG CGG TGC AGC ATC TGC AGC AAC CGG ACC TGC TGG CGG ATC TGC AAA - 3'

- 22 -

Information for SEQ ID NO: 16 G4AδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 17 amino acids, 42 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

171 173 176 182 186 187
N - Val Pro Ser Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile Ser Lys - C
5' - GTG CCT AGC AGC ATC TGC AGC AAC AAC CCG ACC TCC TGG GGG ATC AGC AAA - 3'

Information for SEQ ID NO: 17 G4B

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 17 amino acids, 42 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

171 173 176 182 186 187
N - Val Pro Cys Ser Ile Cys Gly Asn Asn Gln Leu Cys Lys Ser Ile Cys Lys - C
5' - GTG CCC TGC AGC ATC TGC GGC AAC AAC CAG CTG TGC AAA AGC ATC TGC AAA - 3'

Information for SEQ ID NO: 18 G4BδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 17 amino acids, 42 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

171 173 176 182 186 187
N - Val Pro Ser Ser Ile Cys Gly Asn Asn Gln Leu Cys Lys Ser Ile Ser Lys - C
5' - GTG CCC AGC ACC ATC TGC CCC AAC AAC CAG CTG TGC AAA AGC ATC AGC AAA - 3'

Information for SEQ ID NO: 19 G4'A

SEQUENCE TYPE: amino acids

SEQUENCE LENGTH: 17 amino acids

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

171 173 176 182 186 187
N - Val Pro Asp Ser Ile Asp Ser Asn Asn Pro Thr Orn Trp Ala Ile Orn Lys - C

- 23 -

Information for SEQ ID NO: 20 G4'AδC

SEQUENCE TYPE: amino acids

SEQUENCE LENGTH: 17 amino acids

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

171 173 176 182 186 187
N - Val Pro Ser Ser Ile Asp Ser Asn Asn Pro Thr Orn Trp Ala Ile Ser Lys - C

Information for SEQ ID NO: 21 G4'B

SEQUENCE TYPE: amino acids

SEQUENCE LENGTH: 17 amino acids

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

171 173 176 182 186 187
N - Val Pro Asp Ser Ile Asp Gly Asn Asn Gln Leu Orn Lys Ser Ile Orn Lys - C

Information for SEQ ID NO: 22 G4'BδC

SEQUENCE TYPE: amino acids

SEQUENCE LENGTH: 17 amino acids

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

171 173 176 182 186 187
N - Val Pro Ser Ser Ile Asp Gly Asn Asn Gln Leu Orn Lys Ser Ile Ser Lys - C

Information for SEQ ID NO: 23 G200A

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 61 amino acids, 183 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Asn
5' - CAG ACC CAG CCG AGC AAA CCG ACC ACC AAA CAG CGT CAG AAC AAA CCG CCG AAC
158 173 176
Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys
AAA CCG AAC AAC GAT TTC CAT TTC GAA GTG TTC AAC TTC GTG CCG TGC AGC ATC TGC
177 182 186
Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly
AGC AAC AAC CCG ACC TGC TGG CGG ATC TGC AAA CGT ATC CCG AAC AAA AAA CCG GGC
196 200
Lys Lys Thr Thr Thr - C
AAA AAA ACC ACC - 3'

Information for SEQ ID NO: 24 G198A

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 59 amino acids, 177 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Asn
5' - CAG ACC CAG CCG AGC AAA CCG ACC ACC AAA CAG CGT CAG AAC AAA CCG CCG AAC
158 173 176
Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys
AAA CCG AAC AAC GAT TTC CAT TTC GAA GTG TTC AAC TTC GTG CCG TGC AGC ATC TGC
177 182 186
Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly
AGC AAC AAC CCG ACC TGC TGG CGG ATC TGC AAA CGT ATC CCG AAC AAA AAA CCG GGC
196 198
Lys Lys Thr - C
AAA AAA ACC - 3'

Information for SEQ ID NO: 25 G196A

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 57 amino acids, 171 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Asn
5' - CAG ACC CAG CCG AGC AAA CCG ACC ACC AAA CAG CGT CAG AAC AAA CCG CCG AAC
158 173 176
Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys
AAA CCG AAC AAC GAT TTC CAT TTC GAA GTG TTC AAC TTC GTG CCG TGC AGC ATC TGC
177 182 186
Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly
AGC AAC AAC CCG ACC TGC TGG CGG ATC TGC AAA CGT ATC CCG AAC AAA AAA CCG GGC
196
Lys - C
AAA - 3'

Information for SEQ ID NO: 26 G194A

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 55 amino acids, 165 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Asn
5' - CAG ACC CAG CGG AGC AAA CCG ACC ACC AAA CAG CGT CAG AAC AAA CCG CGG AAC
158 173 176
Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys
AAA CGG AAC AAC GAT TTC CAT TTC GAA GTG TTC AAC TTC GTG CGG TGC AGC ATC TGC
177 182 186 194
Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro - C
AGC AAC AAC CGG ACC TGC TGG GCG ATC TGC AAA CGT ATC CGG AAC AAA CGG - 3'

Information for SEQ ID NO: 27 G192A

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 52 amino acids, 156 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Asn
5' - CAG ACC CAG CGG AGC AAA CCG ACC ACC AAA CAG CGT CAG AAC AAA CGG CGG AAC
158 173 176
Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys
AAA CGG AAC AAC GAT TTC CAT TTC GAA GTG TTC AAC TTC GTG CGG TGC AGC ATC TGC
177 182 186 192
Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys - C
AGC AAC AAC CGG ACC TGC TGG GCG ATC TGC AAA CGT ATC CGG AAC AAA - 3'

Information for SEQ ID NO: 28 G6A

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 51 amino acids, 153 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Asn
5' - CAG ACC CAG CGG AGC AAA CCG ACC ACC AAA CAG CGT CAG AAC AAA CGG CGG AAC
158 173 176
Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys
AAA CGG AAC AAC GAT TTC CAT TTC GAA GTG TTC AAC TTC GTG CGG TGC AGC ATC TGC

177 182 186 190
Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro - C
AGC AAC AAC CCG ACC TGC TGG GCG ATC TGC AAA CGT ATC CCG - 3'

Information for SEQ ID NO: 29 G7A

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 33 amino acids, 99 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

158 173
N - Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile
5' - AAA CCG AAC AAC GAT TTC CAT TTC GAA GTG TTC AAC TTC GTG CCG TGC AGC ATC
176 182 186 190
Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro - C
TGC AGC AAC AAC CCG ACC TGC TGG GCG ATC TGC AAA CGT ATC CCG - 3'

Information for SEQ ID NO: 30 G200AδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 61 amino acids, 183 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Asn
5' - CAG ACC CAG CCG AGC AAA CCG ACC ACC AAA CAG CGT CAG AAC AAA CCG CCG AAC
158 173 176
Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys
AAA CCG AAC AAC GAT TTC CAT TTC GAA GTG TTC AAC TTC GTG CCG AGC AGC ATC TGC
177 182 186
Ser Asn Asn Pro Thr Cys Trp Ala Ile Ser Lys Arg Ile Pro Asn Lys Lys Pro Gly
AGC AAC AAC CCG ACC TGC TGG GCG ATC AGC AAA CGT ATC CCG AAC AAA AAA CCG GGC
196 200
Lys Lys Thr Thr Thr - C
AAA AAA ACC ACC ACC - 3'

Information for SEQ ID NO: 31 G198AδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 59 amino acids, 177 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Asn
5' - CAG ACC CAG CCG AGC AAA CCG ACC ACC AAA CAG CGT CAG AAC AAA CCG CCG AAC
158 173 176
Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys
AAA CCG AAC AAC GAT TTC CAT TTC GAA GIG TTC AAC TTC GTG CCG AGC AGC ATC TGC
177 182 186
Ser Asn Asn Pro Thr Cys Trp Ala Ile Ser Lys Arg Ile Pro Asn Lys Lys Pro Gly
AGC AAC AAC CCG ACC TGC TGG GCG ATC AGC AAA CGT ATC CCG AAC AAA AAA CCG GGC
196 198
Lys Lys Thr - C
AAA AAA ACC - 3'

Information for SEQ ID NO: 32 G196AδC

SEQUENCE TYPE: amino acids and nucleotides
SEQUENCE LENGTH: 57 amino acids, 171 nucleotides
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: protein

140
N - Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Asn
5' - CAG ACC CAG CCG AGC AAA CCG ACC ACC AAA CAG CGT CAG AAC AAA CCG CCG AAC
158 173 176
Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys
AAA CCG AAC AAC GAT TTC CAT TTC GAA GIG TTC AAC TTC GTG CCG AGC AGC ATC TGC
177 182 186
Ser Asn Asn Pro Thr Cys Trp Ala Ile Ser Lys Arg Ile Pro Asn Lys Lys Pro Gly
AGC AAC AAC CCG ACC TGC TGG GCG ATC AGC AAA CGT ATC CCG AAC AAA AAA CCG GGC
196
Lys - C
AAA - 3'

Information for SEQ ID NO: 33 G194AδC

SEQUENCE TYPE: amino acids and nucleotides
SEQUENCE LENGTH: 55 amino acids, 165 nucleotides
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: protein

140
N - Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Asn
5' - CAG ACC CAG CCG AGC AAA CCG ACC ACC AAA CAG CGT CAG AAC AAA CCG CCG AAC
158 173 176
Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys
AAA CCG AAC AAC GAT TTC CAT TTC GAA GIG TTC AAC TTC GTG CCG AGC AGC ATC TGC
177 182 186 194
Ser Asn Asn Pro Thr Cys Trp Ala Ile Ser Lys Arg Ile Pro Asn Lys Lys Pro - C
AGC AAC AAC CCG ACC TGC TGG GCG ATC AGC AAA CGT ATC CCG AAC AAA AAA CCG - 3'

Information for SEQ ID NO: 34 G192AδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 52 amino acids, 156 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Asn
5' - CAG ACC CAG CCG AGC AAA CCG ACC ACC AAA CAG CGT CAG AAC AAA CCG CCG AAC
158 173 176
Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys
AAA CCG AAC AAC GAT TTC CAT TTC GAA GTG TTC AAC TIC GTG CCG AGC AGC ATC TGC
177 182 186 192
Ser Asn Asn Pro Thr Cys Trp Ala Ile Ser Lys Arg Ile Pro Asn Lys - C
AGC AAC AAC CCG ACC TGC TGG CCG ATC AGC AAA CGT ATC CCG AAC AAA - 3'

Information for SEQ ID NO: 35 G6AδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 50 amino acids, 150 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Asn
5' - CAG ACC CAG CCG AGC AAA CCG ACC ACC AAA CAG CGT CAG AAC AAA CCG CCG AAC
158 173 176
Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys
AAA CCG AAC AAC GAT TTC CAT TTC GAA GTG TTC AAC TIC GTG CCG AGC AGC ATC TGC
177 182 186 190
Ser Asn Asn Pro Thr Cys Trp Ala Ile Ser Lys Arg Ile Pro - C
AGC AAC AAC CCG ACC TGC TGG CCG ATC AGC AAA CGT ATC CCG - 3'

Information for SEQ ID NO: 36 G7AδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 33 amino acids, 99 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

158 173
N - Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile
5' - AAA CCG AAC AAC GAT TTC CAT TTC GAA GTG TTC AAC TIC GTG CCG AGC AGC ATC
176 182 186 190
Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile Ser Lys Arg Ile Pro - C
TGC AGC AAC AAC CCG ACC TGC TGG CCG ATC AGC AAA CGT ATC CCG - 3'

Information for SEQ ID NO: 37 G200B

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 61 amino acids, 183 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Ser Arg Ser Lys Asn Pro Pro Lys Lys Pro
5' - AGC ACC CAG ACC AAC AAA CCG AGC ACC AAA ACC CGT ACC AAA AAC CCG CCG AAA AAA CCG
160
173 176
Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln
AAA GAT GAT TAC CAC TTC GAA GIG TIC AAC TTC GTG CCC TGC ACC ATC TGC GCC AAC AAC CAG
182 186 200
Leu Cys Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys Pro Thr Ile - C
CTG TGC AAA AGC ATC TGC AAA ACC ATC CCG AGC AAC AAA CCG AAA AGC AAA CCG ACC ATC - 3'

Information for SEQ ID NO: 38 G198B

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 59 amino acids, 177 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Ser Arg Ser Lys Asn Pro Pro Lys Lys Pro
5' - AGC ACC CAG ACC AAC AAA CCG AGC ACC AAA ACC CGT ACC AAA AAC CCG CCG AAA AAA CCG
160
173 176
Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln
AAA GAT GAT TAC CAC TTC GAA GIG TIC AAC TTC GTG CCC TGC ACC ATC TGC GCC AAC AAC CAG
182 186 198
Leu Cys Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys Pro - C
CTG TGC AAA AGC ATC TGC AAA ACC ATC CCG AGC AAC AAA CCG AAA AAG AAA CCG - 3'

Information for SEQ ID NO: 39 G196B

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 57 amino acids, 171 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Ser Arg Ser Lys Asn Pro Pro Lys Lys Pro
5'- ACC ACC CAG ACC AAC AAA CGG ACC ACC AAA ACC CGT ACC AAA AAC CGG CGG AAA AAA CGG
160 173 176
Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln
AAA GAT GAT TAC CAC TIC GAA GIG TIC AAC TIC GIG CGC TCC AGC ATC TCC GGC AAC AAC CAG
182 186 196
Leu Cys Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys - C
CTG TCC AAA ACC ATC TCC AAA ACC ATC CGG ACC AAC AAA CGG AAA AAG - 3'

Information for SEQ ID NO: 40 G194B

SEQUENCE TYPE: amino acids and nucleotides
SEQUENCE LENGTH: 55 amino acids, 165 nucleotides
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: protein

140
N - Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Ser Arg Ser Lys Asn Pro Pro Lys Lys Pro
5'- ACC ACC CAG ACC AAC AAA CGG ACC ACC AAA ACC CGT ACC AAA AAC CGG CGG AAA AAA CGG
160 173 176
Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln
AAA GAT GAT TAC CAC TIC GAA GIG TIC AAC TIC GIG CGC TCC AGC ATC TCC GGC AAC AAC CAG
182 186 191
Leu Cys Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys Pro - C
CTG TCC AAA ACC ATC TCC AAA ACC ATC CGG ACC AAC AAA CGG - 3'

Information for SEQ ID NO: 41 G192B

SEQUENCE TYPE: amino acids and nucleotides
SEQUENCE LENGTH: 53 amino acids, 159 nucleotides
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: protein

140
N - Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Ser Arg Ser Lys Asn Pro Pro Lys Lys Pro
5'- ACC ACC CAG ACC AAC AAA CGG ACC ACC AAA ACC CGT ACC AAA AAC CGG CGG AAA AAA CGG
160 173 176
Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln
AAA GAT GAT TAC CAC TIC GAA GIG TIC AAC TIC GIG CGC TCC AGC ATC TCC GGC AAC AAC CAG
182 186 192
Leu Cys Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn - C
CTG TCC AAA ACC ATC TCC AAA ACC ATC CGG ACC AAC AAA CGG - 3'

Information for SEQ ID NO: 42 G6B

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 51 amino acids, 153 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140

N - Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Ser Arg Ser Lys Asn Pro Pro Lys Pro
5' - AGC ACC CAG ACC AAC AAA CCG ACC ACC AAA AGC CCG ACC AAA AAC CCG CCG AAA AAA CCG
160 173 176
Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln
AAA GAT GAT TAC CAC TTC GAA GTG TTC AAC TTC GTG CCC TCC AGC ATC TCC GGC AAC AAC CAG
182 186 190
Leu Cys Lys Ser Ile Cys Lys Thr Ile Pro - C
CTG TGC AAA AGC ATC TCC AAA ACC ATC CCG - 3'

Information for SEQ ID NO: 43 G7B

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 33 amino acids, 99 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

158

173 176

N - Lys Pro Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly
5' - AAA CCG AAA GAT GAT TAC CAC TTC GAA GTG TTC AAC TTC GTG CCC TCC AGC ATC TCC CCC
182 186 190
Asn Asn Gln Leu Cys Lys Ser Ile Cys Lys Thr Ile Pro - C
AAC AAC CAG CTG TCC AAA AGC ATC TCC AAA ACC ATC CCG - 3'

Information for SEQ ID NO: 44 G200BdC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 61 amino acids, 183 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140

N - Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Ser Arg Ser Lys Asn Pro Pro Lys Pro
5' - AGC ACC CAG ACC AAC AAA CCG ACC ACC AAA AGC CCG ACC AAA AAC CCG CCG AAA AAA CCG
160 173 176
Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys Gly Asn Asn Gln
AAA GAT GAT TAC CAC TTC GAA GTG TTC AAC TTC GTG CCC AGC ACC ATC TCC GGC AAC AAC CAG
182 186 200
Leu Cys Lys Ser Ile Ser Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Pro Thr Ile - C
CTG TGC AAA AGC ATC ACC AAA ACC ATC CCG AAC AAA CCG AAA AGG AAA CCG ACC ATC - 3'

Information for SEQ ID NO: 45 G198BδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 59 amino acids, 177 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Ser Arg Ser Lys Asn Pro Pro Lys Lys Pro
5' - AGC ACC CAG ACC AAC AAA CCG ACC ACC AAA AGC CGT AGC AAA AAC CCG CCG AAA AAA CCG
160 173 176
Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys Gly Asn Asn Gln
AAA GAT GAT TAC CAC TTC GAA GIG TTC AAC TTC GTG CCC AGC AGC ATC TGC GGC AAC AAC CAG
182 186 196
Leu Cys Lys Ser Ile Ser Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys Pro - C
CTG TGC AAA AGC ATC AGC AAA ACC ATC CCG AGC AAC AAA CCG AAA AAG AAA CCG - 3'

Information for SEQ ID NO: 46 G196BδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 57 amino acids, 171 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Ser Arg Ser Lys Asn Pro Pro Lys Lys Pro
5' - AGC ACC CAG ACC AAC AAA CCG ACC ACC AAA AGC CGT AGC AAA AAC CCG CCG AAA AAA CCG
160 173 176
Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys Gly Asn Asn Gln
AAA GAT GAT TAC CAC TTC GAA GIG TTC AAC TTC GTG CCC AGC AGC ATC TGC GGC AAC AAC CAG
182 186 196
Leu Cys Lys Ser Ile Ser Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys Pro - C
CTG TGC AAA AGC ATC AGC AAA ACC ATC CCG AGC AGC AAC AAA CCG AAA AAG - 3'

Information for SEQ ID NO: 47 G194BδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 55 amino acids, 165 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140

N - Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Ser Arg Ser Lys Asn Pro Pro Lys Lys Pro
5'- AGC ACC CAG ACC AAC AAA CCG ACC ACC AAA AGC CGT ACC AAA AAC CCG CCG AAA AAA CCG
160 173 176
Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys Gly Asn Asn Gln
AAA GAT GAT TAC CAC TTC GAA GTG TTC AAC TTC GTG CCC AGC AGC ATC TGC GGC AAC AAC AAC CAG
182 186 194
Leu Cys Lys Ser Ile Ser Lys Thr Ile Pro Ser Asn Lys Pro - C
CTG TGC AAA AGC ATC ACC AAA ACC ATC CCG AGC AAC AAA CCG - 3'

Information for SEQ ID NO: 48 G192BδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 53 amino acids, 159 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140

N - Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Ser Arg Ser Lys Asn Pro Pro Lys Lys Pro
5'- AGC ACC CAG ACC AAC AAA CCG ACC ACC AAA AGC CGT ACC AAA AAC CCG CCG AAA AAA CCG
160 173 176
Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys Gly Asn Asn Gln
AAA GAT GAT TAC CAC TTC GAA GTG TTC AAC TTC GTG CCC AGC AGC ATC TGC GGC AAC AAC AAC CAG
182 186 192
Leu Cys Lys Ser Ile Ser Lys Thr Ile Pro Ser Asn - C
CTG TGC AAA AGC ATC ACC AAA ACC ATC CCG AGC AAC - 3'

Information for SEQ ID NO: 49 G6BδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 51 amino acids, 153 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140

N - Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Ser Arg Ser Lys Asn Pro Pro Lys Lys Pro
5'- AGC ACC CAG ACC AAC AAA CCG ACC ACC AAA AGC CGT ACC AAA AAC CCG CCG AAA AAA CCG
160 173 176
Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys Gly Asn Asn Gln
AAA GAT GAT TAC CAC TTC GAA GTG TTC AAC TTC GTG CCC AGC AGC ATC TGC GGC AAC AAC AAC CAG

182 186 190

Leu Cys Lys Ser Ile Ser Lys Thr Ile Pro - C
CTG TGC AAA AGC ATC ACC AAA ACC ATC CCG - 3'

Information for SEQ ID NO: 50 G7BδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 33 amino acids, 99 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

158 173 176
N - Lys Pro Lys Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Ser Ser Ile Cys Gly
5' - AAA CCG AAA GAT GAT TAC CAC TTC GAA GTG TTC AAC TTC GTG CCC ACC ACC ATC TCC GGC
182 186 190
Asn Asn Gln Leu Cys Lys Ser Ile Ser Lys Thr Ile Pro - C
AAC AAC CAG CTG TGC AAA AGC ATC ACC AAA ACC ATC CCG - 3'

Information for SEQ ID NO: 51 G2V

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 101 amino acids, 303 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

130
N - Gln Asn Arg Lys Ile Lys Gly Gln Ser Thr Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn
5' - CAA AAC AGA AAA ATC AAA GGT CAA TCA ACA CTA CCA GGC ACA AGA AAA CCA CCA ATT AAT
150
Pro Ser Gly Ser Ile Pro Pro Glu Asn His Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr
CCA TCA GCA AGC ATC CCA CCA GAA AAC CAT CAA GAC CAC AAC AAC TTC CAA ACA CTC CCC TAT
171 173 176 182 186
Val Pro Cys Ser Thr Cys Glu Gly Asn Leu Ala Cys Leu Ser Leu Cys His Ile Glu Thr Glu
GTT CCC TGC AGT ACA TGT GAA GGT ATT CTT GCA TGC TTA TCA CTC TGC CAT ATT GAG AGG GAA
192
Arg Ala Pro Ser Arg Ala Pro Thr Ile Thr Leu Lys Lys Thr Pro Lys Pro Lys Thr Thr Lys
AGA GCA CCA AGC AGA GCA CCA ACA ATC ACC CTC AAA AAG ACA CCA AAA CCA AAA ACC ACA AAA
213
230
Lys Pro Thr Lys Thr Thr Ile His His Arg Thr Ser Pro Glu Thr Lys Leu Gln - C
AAG CCA ACC AAG ACA ATC CAT CAC AGA ACC AGC CCA GAA ACC AAA CTG CAA - 3'

Information for SEQ ID NO: 52 G2VδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 101 amino acids, 303 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

130
N - Gln Asn Arg Lys Ile Lys Gly Gln Ser Thr Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn
5' - CAA AAC AGA AAA ATC AAA GGT CAA TCA ACA CTA CCA GGC ACA AGA AAA CCA CCA ATT AAT

150
Pro Ser Gly Ser Ile Pro Pro Glu Asn His Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr
CCA TCA GGA AGC ATC CCA CCA GAA AAC CAT CAA GAC CAC AAC TTC CAA ACA CTC CCC TAT
171 173 176 182 186
Val Pro Ser Ser Thr Cys Glu Gly Asn Leu Ala Cys Leu Ser Leu Ser His Ile Glu Thr Glu
GTT CCC AGC AGT ACA TGT GAA GGT AAT CTT GCA TCC TTA TCA CTC AGC CAT ATT GAG ACG GAA
192
Arg Ala Pro Ser Arg Ala Pro Thr Ile Thr Leu Lys Lys Thr Pro Lys Pro Lys Thr Thr Lys
AGA GCA CCA ACC AGA GCA CCA ACA ATC ACC CTC AAA AAG ACA CCA AAA CCA ACC ACA AAA
213 230
Lys Pro Thr Lys Thr Thr Ile His His Arg Thr Ser Pro Glu Thr Lys Leu Gln - C
AAG CCA ACC AAG ACA ACA ATC CAT CTC AGA ACC ACC CCA GAA ACC ACC CTG CAA - 3'

Information for SEQ ID NO: 53 G200V

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 61 amino acids, 183 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn Pro Ser Gly Ser Ile Pro Pro Glu Asn His
5' - CTA CCA GCC ACA AGA AAA CCA CCA ATT AAT CCA TCA GGA AGC ATC CCA CCA GAA AAC CAT
160 173 176
Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Cys Ser Thr Cys Glu Gly Asn Leu
CAA GAC CAC AAC AAC TTC CAA ACA CTC CCC TAT GTT CCC TCC AGT ACA TGT GAA GGT AAT CTT
182 186 200
Ala Cys Leu Ser Leu Cys His Ile Glu Thr Glu Arg Ala Pro Ser Arg Ala Pro Thr Ile - C
GCA TCC TTA TCA CTC TCC CAT ATT GAG AGA GCA ACC AGA GCA CCA ACA ATC - 3'

Information for SEQ ID NO: 54 G198V

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 59 amino acids, 177 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

Information for SEQ ID NO: 55 G196V

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 57 amino acids, 171 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140

N - Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn Pro Ser Gly Ser Ile Pro Pro Glu Asn His
5'- CTA CCA GGC ACA AGA AAA CCA CCA ATT AAT CCA TCA GGA AGC ATC CCA CCA GAA AAC CAT
160 173 176
Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Cys Ser Thr Cys Glu Gly Asn Leu
CAA GAC CAC AAC AAC TTC CAA ACA CTC CCC TAT GTT CCC TGC AGT ACA TGT GAA GGT ATT CTT
182 186 196
Ala Cys Leu Ser Leu Cys His Ile Glu Thr Glu Arg Ala Pro Ser Arg - C
GCA TGC TTA TCA CTC TCC CAT ATT GAG GAA AGA GCA AGC AGA - 3'

Information for SEQ ID NO: 56 G194V

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 55 amino acids, 165 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140

N - Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn Pro Ser Gly Ser Ile Pro Pro Glu Asn His
5'- CTA CCA GGC ACA AGA AAA CCA CCA ATT AAT CCA TCA GGA AGC ATC CCA CCA GAA AAC CAT
160 173 176
Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Cys Ser Thr Cys Glu Gly Asn Leu
CAA GAC CAC AAC AAC TTC CAA ACA CTC CCC TAT GTT CCC TGC AGT ACA TGT GAA GGT ATT CTT
182 186 194
Ala Cys Leu Ser Leu Cys His Ile Glu Thr Glu Arg Ala Pro - C
GCA TGC TTA TCA CTC TCC CAT ATT GAG GAA AGA GCA AGC AGA - 3'

Information for SEQ ID NO: 57 G192V

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 52 amino acids, 156 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140

N - Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn Pro Ser Gly Ser Ile Pro Pro Glu Asn His
5'- CTA CCA GGC ACA AGA AAA CCA CCA ATT AAT CCA TCA GGA AGC ATC CCA CCA GAA AAC CAT
160 173 176
Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Cys Ser Thr Cys Glu Gly Asn Leu
CAA GAC CAC AAC AAC TTC CAA ACA CTC CCC TAT GTT CCC TGC AGT ACA TGT GAA GGT ATT CTT
182 186 192
Ala Cys Leu Ser Leu Cys His Ile Glu Thr Glu Arg - C
GCA TGC TTA TCA CTC TCC CAT ATT GAG GAA AGA - 3'

Information for SEQ ID NO: 58 G6V

SEQUENCE LENGTH: 51 amino acids, 153 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn Pro Ser Gly Ser Ile Pro Pro Glu Asn His
5' - CTA CCA GGC ACA AGA AAA CCA CCA ATT AAT CCA TCA GGA AGC ATC CCA CCA GAA AAC CAT
160 173 176
Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Cys Ser Thr Cys Glu Gly Asn Leu
CAA GAC CAC AAC AAC TTC CAA ACA CTC CCC TAT GTT CCC TCC AGT ACA TGT GAA GGT AAT CTT
182 186 190
Ala Cys Leu Ser Leu Cys His Ile Glu Thr - C
GCA TGC TTA TCA CTC TGC CAT ATT GAG ACG - 3'

Information for SEQ ID NO: 59 G7V

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 33 amino acids, 99 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

158 173 176
N - Asn His Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Cys Ser Thr Cys
5' - AAC CAT CAA GAC CAC AAC AAC TTC CAA ACA CTC CCC TAT GTT CCC TCC AGT ACA TGT
182 186 190
Glu Gly Asn Leu Ala Cys Leu Ser Leu Cys His Ile Glu Thr - C
GAA GGT AAT CTT GCA TGC TTA TCA CTC TGC CAT ATT GAG ACG - 3'

Information for SEQ ID NO: 60 G200VδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 61 amino acids, 183 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn Pro Ser Gly Ser Ile Pro Pro Glu Asn His
5' - CTA CCA GGC ACA AGA AAA CCA CCA ATT AAT CCA TCA GGA AGC ATC CCA CCA GAA AAC CAT
160 173 176
Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Ser Ser Thr Cys Glu Gly Asn Leu
CAA GAC CAC AAC AAC TTC CAA ACA CTC CCC TAT GTT CCC AGC AGT ACA TGT GAA GGT AAT CTT
182 186 200
Ala Cys Leu Ser Leu Ser His Ile Glu Thr Glu Arg Ala Pro Ser Arg Ala Pro Thr Ile - C
GCA TGC TTA TCA CTC AGC CAT ATT GAG ACG GAA AGA GCA ACC AGA GCA ACC AGA ATC - 3'

Information for SEQ ID NO: 61 G198VδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 59 amino acids, 177 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn Pro Ser Gly Ser Ile Pro Pro Glu Asn His
5'- CTA CCA GGC ACA AGA AAA CCA CCA ATT AAT CCA TCA GGA AGC ATC CCA CCA GAA AAC CAT
160 173 176
Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Ser Ser Thr Cys Glu Gly Asn Leu
CAA GAC CTC AAC AAC TTC CAA ACA CTC CCC TAT GTT CCC AGC AGT ACA TGT GAA GGT AAT CTT
182 186 196
Ala Cys Leu Ser Leu Ser His Ile Glu Thr Glu Arg Ala Pro Ser Arg Ala Pro - C
GCA TGC TTA TCA CTC ACC CAT ATT GAG ACG GAA AGA CCA ACC AGA GCA CCA - 3'

Information for SEQ ID NO: 62 G196VδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 57 amino acids, 171 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140
N - Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn Pro Ser Gly Ser Ile Pro Pro Glu Asn His
5'- CTA CCA GGC ACA AGA AAA CCA CCA ATT AAT CCA TCA GGA AGC ATC CCA CCA GAA AAC CAT
160 173 176
Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Ser Ser Thr Cys Glu Gly Asn Leu
CAA GAC CTC AAC AAC TTC CAA ACA CTC CCC TAT GTT CCC AGC AGT ACA TGT GAA GGT AAT CTT
182 186 196
Ala Cys Leu Ser Leu Ser His Ile Glu Thr Glu Arg Ala Pro Ser Arg - C
GCA TGC TTA TCA CTC ACC CAT ATT GAG ACG GAA AGA CCA ACC AGA GCA - 3'

Information for SEQ ID NO: 63 G194VδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 55 amino acids, 165 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140

N - Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn Pro Ser Gly Ser Ile Pro Pro Glu Asn His
5' - CTA CCA GCC ACA AGA AAA CCA CCA ATT AAT CCA TCA GGA AGC ATC CCA CCA GAA AAC CAT
160 173 176
Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Ser Ser Thr Cys Glu Gly Asn Leu
CAA GAC CAC AAC AAC TTC CAA ACA CTC CCC TAT GGT CCC AGC AGT ACA TGT GAA GGT AAT CTT
182 186 194
Ala Cys Leu Ser Leu Ser His Ile Glu Thr Glu Arg Ala Pro - C
GCA TGC TTA TCA CTC AGC CAT ATT GAG ACG GAA AGA CCA CCA - 3'

Information for SEQ ID NO: 64 G192VδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 52 amino acids, 156 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140

N - Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn Pro Ser Gly Ser Ile Pro Pro Glu Asn His
5' - CTA CCA GCC ACA AGA AAA CCA CCA ATT AAT CCA TCA GGA AGC ATC CCA CCA GAA AAC CAT
160 173 176
Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Ser Ser Thr Cys Glu Gly Asn Leu
CAA GAC CAC AAC AAC TTC CAA ACA CTC CCC TAT GGT CCC AGC AGT ACA TGT GAA GGT AAT CTT
182 186 192
Ala Cys Leu Ser Leu Ser His Ile Glu Thr Glu Arg - C
GCA TGC TTA TCA CTC AGC CAT ATT GAG ACG GAA AGA - 3'

Information for SEQ ID NO: 65 G6VδC

SEQUENCE LENGTH: 51 amino acids, 153 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

140

N - Leu Pro Ala Thr Arg Lys Pro Pro Ile Asn Pro Ser Gly Ser Ile Pro Pro Glu Asn His
5' - CTA CCA GCC ACA AGA AAA CCA CCA ATT AAT CCA TCA GGA AGC ATC CCA CCA GAA AAC CAT
160 173 176
Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Ser Ser Thr Cys Glu Gly Asn Leu
CAA GAC CAC AAC AAC TTC CAA ACA CTC CCC TAT GGT CCC AGC AGT ACA TGT GAA GGT AAT CTT
182 186 190
Ala Cys Leu Ser Leu Ser His Ile Glu Thr - C
GCA TGC TTA TCA CTC AGC CAT ATT GAG ACG - 3'

Information for SEQ ID NO: 66 G7VδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 33 amino acids, 99 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

158 173 176
N - Asn His Gln Asp His Asn Asn Phe Gln Thr Leu Pro Tyr Val Pro Ser Ser Thr Cys
5' - AAC CAT CAA GAC CAC AAC AAC TTC CAA ACA CTC CTC TAT GTC CCC AGC AGT ACA TGT
182 186 190
Glu Gly Asn Leu Ala Cys Leu Ser Leu Ser His Ile Glu Thr - C
GAA GGT AAT CTT GCA TGC TTA TCA CTC ACC CAT ATT GPG AGG - 3'

Information for SEQ ID NO: 67 G4V

SEQUENCE TYPE: amino acids and nucleotides
SEQUENCE LENGTH: 17 amino acids, 51 nucleotides
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: peptide

171 173 176 182 186 187
N - Val Pro Cys Ser Thr Cys Glu Gly Asn Leu Ala Cys Leu Ser Leu Cys His - C
5' - GIT CCC TGC AGT ACA TGT GAA GGT AAT CTT GCA TGC TTA TCA CTC TGC CAT - 3'

Information for SEQ ID NO: 68 G4VδC

SEQUENCE TYPE: amino acids and nucleotides
SEQUENCE LENGTH: 17 amino acids, 51 nucleotides
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: peptide

171 173 176 182 186 187
N - Val Pro Ser Ser Thr Cys Glu Gly Asn Leu Ala Cys Leu Ser Leu Ser His - C
5' - GIT CCC AGC AGT ACA TGT GAA GGT AAT CTT GCA TGC TTA TCA CTC AGC CAT - 3'

Information for SEQ ID NO: 69 G4'V

SEQUENCE TYPE: amino acids
SEQUENCE LENGTH: 17 amino acids
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: peptide

171 173 176 182 186 187
N - Val Pro Asp Ser Thr Asp Glu Gly Asn Leu Ala Cys Leu Ser Leu Cys His - C

Information for SEQ ID NO: 70 G4'VδC

SEQUENCE TYPE: amino acids
SEQUENCE LENGTH: 17 amino acids
STRANDEDNESS: single
TOPOLOGY: linear

MOLECULE TYPE: peptide

171 173 176 182 186 187
N - Val Pro Ser Ser Thr Asp Glu Gly Asn Leu Ala Cys Leu Ser Leu Ser His - C

Information for SEQ ID NO: 71 G1V

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 14 amino acids 42 nucleotides

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

174 176 182 186 187
N - Ser Thr Cys Glu Gly Asn Leu Ala Cys Leu Ser Leu Cys His - C
5' - AGT ACA TGT GAA GGT AAT CTT GCA TGC TTA TCA CTC TGC CAT - 3'

Information for SEQ ID NO: 72 G1VδC

SEQUENCE TYPE: amino acids and nucleotides

SEQUENCE LENGTH: 14 amino acids,

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

174 176 182 186 187
N - Ser Thr Cys Glu Gly Asn Leu Ala Cys Leu Ser Leu Ser His - C
5' - AGT ACA TGT GAA GGT AAT CTT GCA TGC TTA TCA CTC AGC CAT - 3'

Information for SEQ ID NO: 73 G1'VδC

SEQUENCE TYPE: amino acids

SEQUENCE LENGTH: 14 amino acids

STRANDEDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

174 176 182 186 187
N - Ser Thr Asp Glu Gly Asn Leu Ala Cys Leu Ser Leu Ser His - C

CLAIMS

1. Use of at least one fragment of an enterobacterium membrane protein OmpA for preparing a pharmaceutical composition intended to be administered nasally, to improve the immunity of a mammal with respect to an antigen or to a hapten.
2. Use of at least one fragment of a membrane protein of Klebsiella for preparing a pharmaceutical composition intended to be administered nasally, to improve the immunity of a mammal with respect to an antigen or to a hapten.
3. Use of at least one fragment of a membrane protein according to claim 2, characterized in that the membrane protein is an OmpA of Klebsiella *pneumoniae*.
4. Use of at least one fragment of a membrane protein according to one of claims 1 to 3, characterized in that said membrane protein or its fragment is obtained by recombinant process.
5. Use of at least one fragment of a membrane protein according to claim 4, characterized in that said recombinant membrane protein or its fragment is renatured in the presence of detergent chosen from Zwittergent 3-14, Zwittergent 3-12 and octylglucopyranoside.
6. Use of at least one fragment of a membrane protein according to one of claims 1 to 5, characterized in that at least one fragment has the sequence SEQ ID No 1.
7. Use according to one of claims 1 to 6, characterized in that the antigen or the hapten are [sic] chosen from the group comprising proteins, peptides, polysaccharides, oligosaccharides and nucleic acids.
8. Use of at least one fragment of a membrane protein according to one of claims 1 to 7, characterized in that the antigen or the hapten originate from a virus or from a bacterium.

9. Use of at least one fragment of a membrane protein according to one of claims 1 to 8, characterized in that the antigen or the hapten comprises at least one protein fragment of a 5 microorganism responsible for pathologies of the airways.

10. Use according to claim 9, characterized in that said microorganism responsible for pathologies of the airways is chosen from RSV, parainfluenzae virus (PIV), 10 influenza virus, hantavirus, streptococci, pneumococci and meningococci.

11. Use of at least one fragment of a membrane protein according to one of claims 1 to 10, characterized in that the antigen or the hapten 15 comprises at least one protein fragment of the human or bovine respiratory syncytial virus (RSV).

12. Use according to claim 11, characterized in that the antigen or hapten comprises at least one fragment of the protein G of the RSV.

20 13. Use according to either of claims 11 and 12, characterized in that the antigen or the hapten comprises at least one of the sequences SEQ ID No 2 to SEQ ID No 73.

14. Use according to one of claims 1 to 13, 25 characterized in that said fragment of a membrane protein is covalently coupled to said antigen or hapten.

15. Use according to claim 14, characterized in that one or more bonding elements is introduced into 30 the fragment of membrane protein and/or of the antigen or of the hapten in order to facilitate the coupling.

16. Use according to claim 15, characterized in that the bonding element introduced is an amino acid.

17. Use according to claim 14, characterized in 35 that the hybrid protein, which is obtained after coupling between the fragment of a membrane protein and the antigen or the hapten, when said antigen or hapten is protein in nature, is prepared by genetic recombination.

18. Use according to one of claims 14 to 17, characterized in that the pharmaceutical composition contains a fragment of a membrane protein coupled to an antigen or a hapten.

5 19. Use according to claim 17, characterized in that the pharmaceutical composition contains a transformed host cell which is capable of expressing a hybrid protein containing said fragment of membrane protein coupled to said antigen or hapten.

10 20. Use according to either of claims 18 and 19, characterized in that the pharmaceutical composition does not contain any adjuvant.

21. Method for preparing a protein or one of its fragments by recombinant process, characterized in that 15 said protein or one of its fragments is, after extraction, renatured in the presence of a solution comprising a detergent chosen from Zwittergent 3-14, Zwittergent 3-12 and octylglucopyranoside, and in that said recombinant protein is not interferon β .

20

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CABINET REGIMBEAU

PATENT ATTORNEYS

ORIGINAL [signature] 26 Avenue Kléber

75116 PARIS

CLAIMS

1. Use of at least one fragment of an enterobacterium membrane protein OmpA for preparing a pharmaceutical composition intended to be administered nasally, to improve the immunity of a mammal with respect to an antigen or to a hapten.
5
2. Use of at least one fragment of a membrane protein of Klebsiella for preparing a pharmaceutical composition intended to be administered nasally, to improve the immunity of a mammal with respect to an antigen or to a hapten.
10
3. Use of at least one fragment of a membrane protein according to claim 2, characterized in that the membrane protein is an OmpA of Klebsiella pneumoniae.
15
4. Use of at least one fragment of a membrane protein according to one of claims 1 to 3, characterized in that said membrane protein or its fragment is obtained by recombinant process.
20
5. Use of at least one fragment of a membrane protein according to claim 4, characterized in that said recombinant membrane protein or its fragment is renatured in the presence of detergent chosen from Zwittergent 3-14, Zwittergent 3-12 and octylglucopyranoside.
25
6. Use of at least one fragment of a membrane protein according to one of claims 1 to 5, characterized in that at least one fragment has the sequence SEQ ID No 1.
30
7. Use according to one of claims 1 to 6, characterized in that the antigen or the hapten are [sic] chosen from the group comprising proteins, peptides, polysaccharides, oligosaccharides and nucleic acids.
35
8. Use of at least one fragment of a membrane protein according to one of claims 1 to 7, characterized in that the antigen or the hapten originate from a virus or from a bacterium.

9. Use of at least one fragment of a membrane protein according to one of claims 1 to 8, characterized in that the antigen or the hapten comprises at least one protein fragment of a 5 microorganism responsible for pathologies of the airways.

10. Use according to claim 9, characterized in that said microorganism responsible for pathologies of the airways is chosen from RSV, parainfluenzae virus (PIV), 10 influenza virus, hantavirus, streptococci, pneumococci and meningococci.

11. Use of at least one fragment of a membrane protein according to one of claims 1 to 10, characterized in that the antigen or the hapten 15 comprises at least one protein fragment of the human or bovine respiratory syncytial virus (RSV).

12. Use according to claim 11, characterized in that the antigen or hapten comprises at least one fragment of the protein G of the RSV.

20 13. Use according to either of claims 11 and 12, characterized in that the antigen or the hapten comprises at least one of the sequences SEQ ID No 2 to SEQ ID No 73.

14. Use according to one of claims 1 to 13, 25 characterized in that said fragment of a membrane protein is covalently coupled to said antigen or hapten.

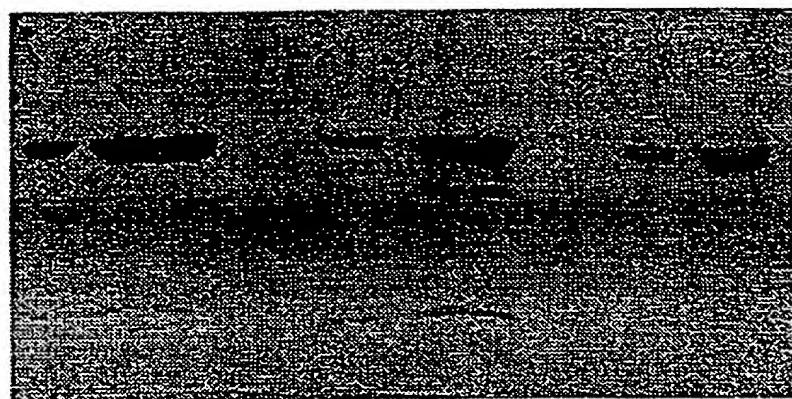
15. Use according to claim 14, characterized in that one or more bonding elements is introduced into 30 the fragment of membrane protein and/or of the antigen or of the hapten in order to facilitate the coupling.

16. Use according to claim 15, characterized in that the bonding element introduced is an amino acid.

17. Use according to claim 14, characterized in 35 that the hybrid protein, which is obtained after coupling between the fragment of a membrane protein and the antigen or the hapten, when said antigen or hapten is protein in nature, is prepared by genetic recombination.

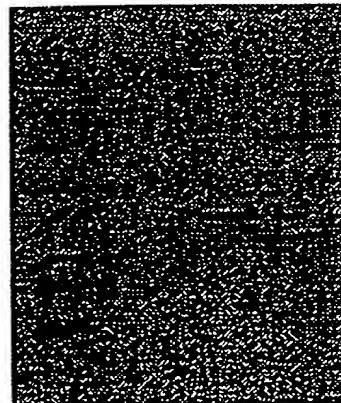
18. Use according to one of claims 14 to 17, characterized in that the pharmaceutical composition contains a fragment of a membrane protein coupled to an antigen or a hapten.
- 5 19. Use according to claim 17, characterized in that the pharmaceutical composition contains a transformed host cell which is capable of expressing a hybrid protein containing said fragment of membrane protein coupled to said antigen or hapten.
- 10 20. Use according to either of claims 18 and 19, characterized in that the pharmaceutical composition does not contain any adjuvant.

A



1 2 3 4 5 6

B



Std 1 2

FIG. 1

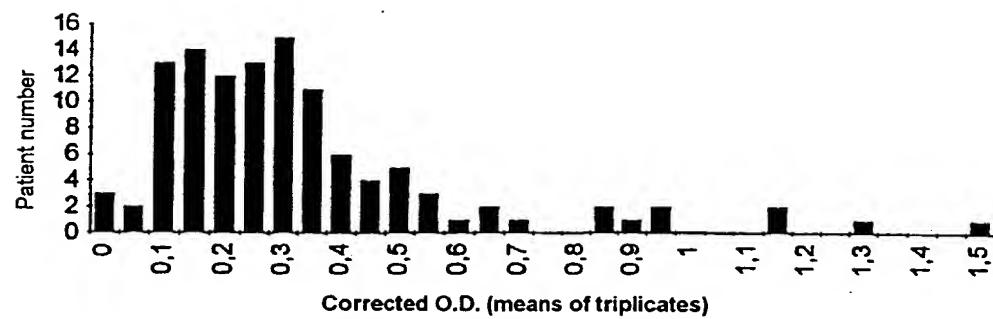


FIG. 2

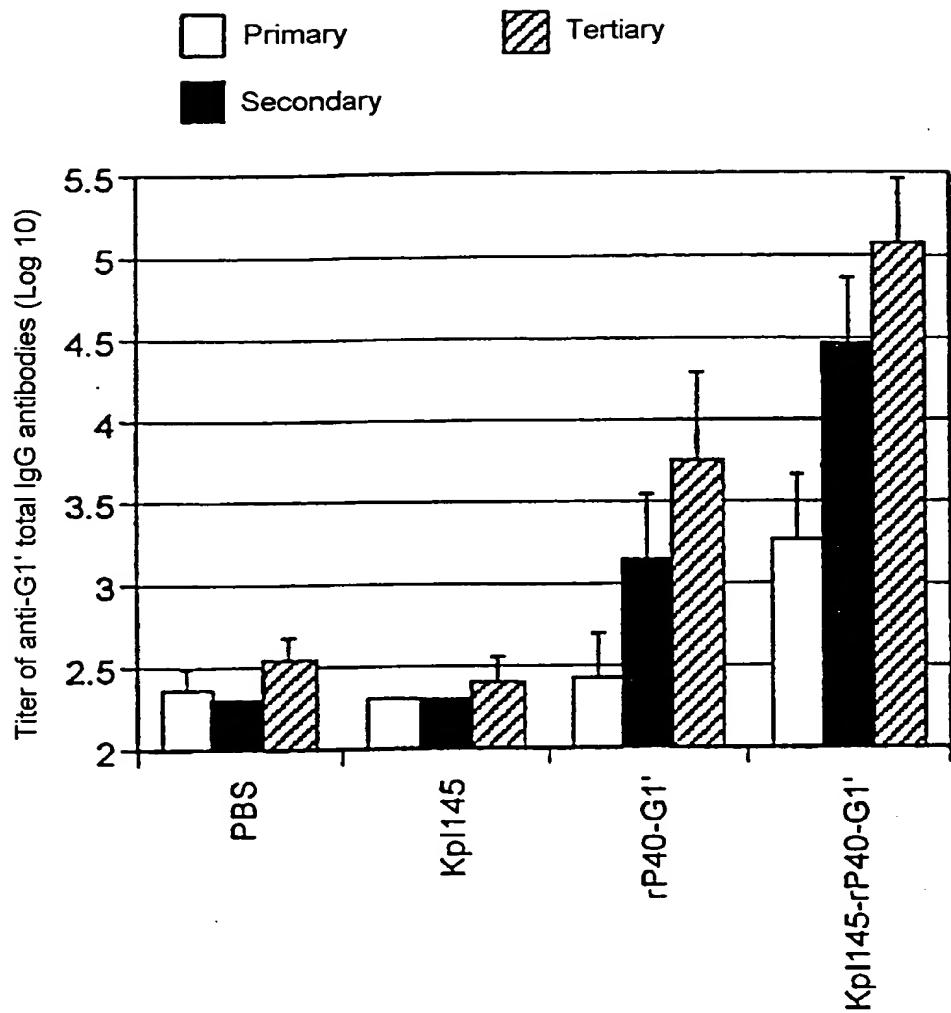


FIG. 3

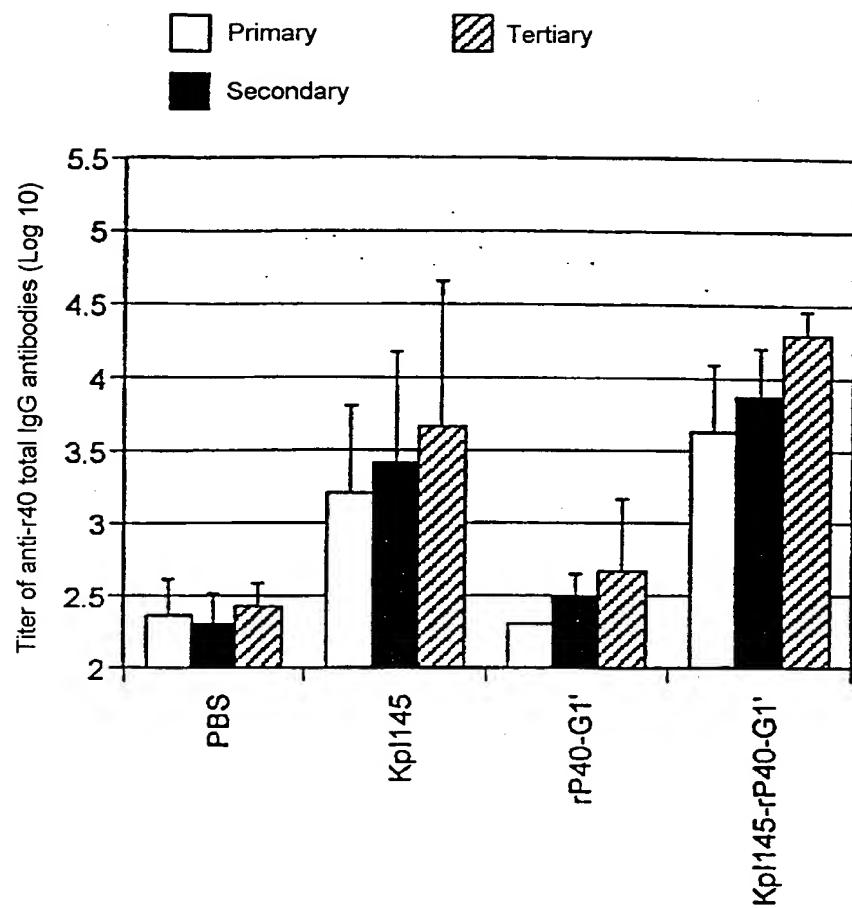


FIG. 4

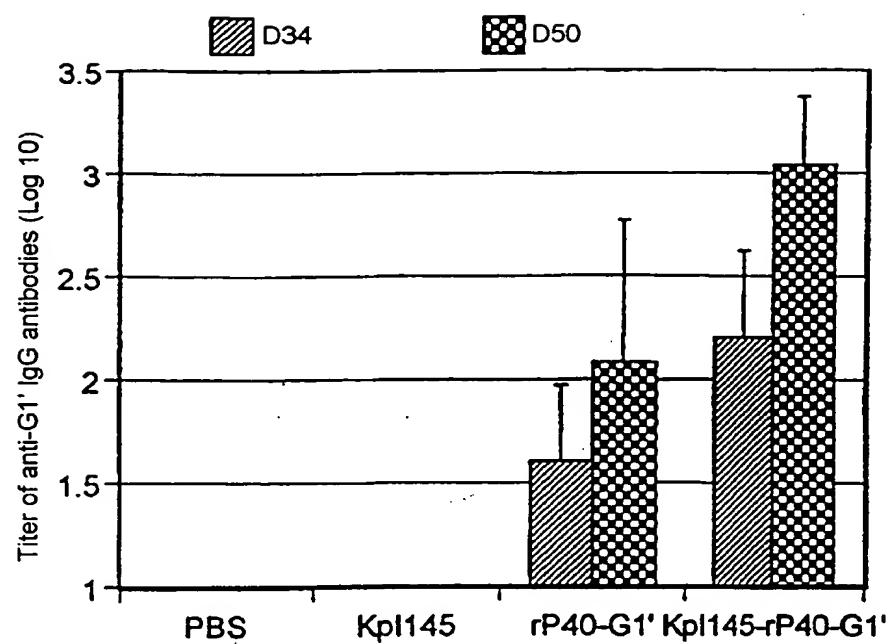


FIG. 5

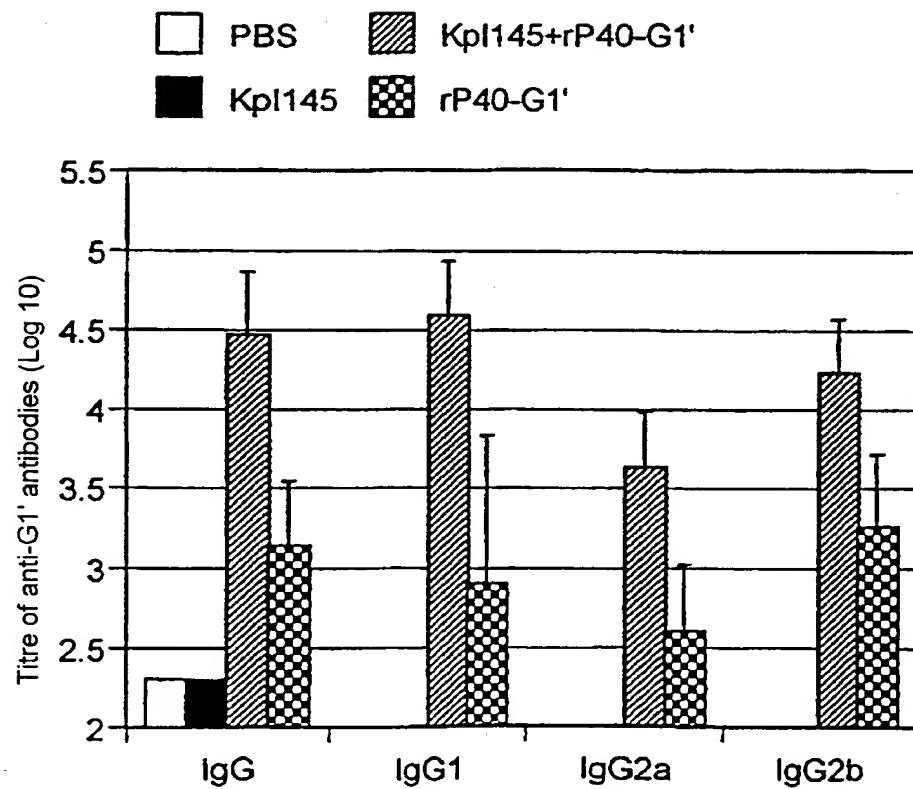


FIG. 6

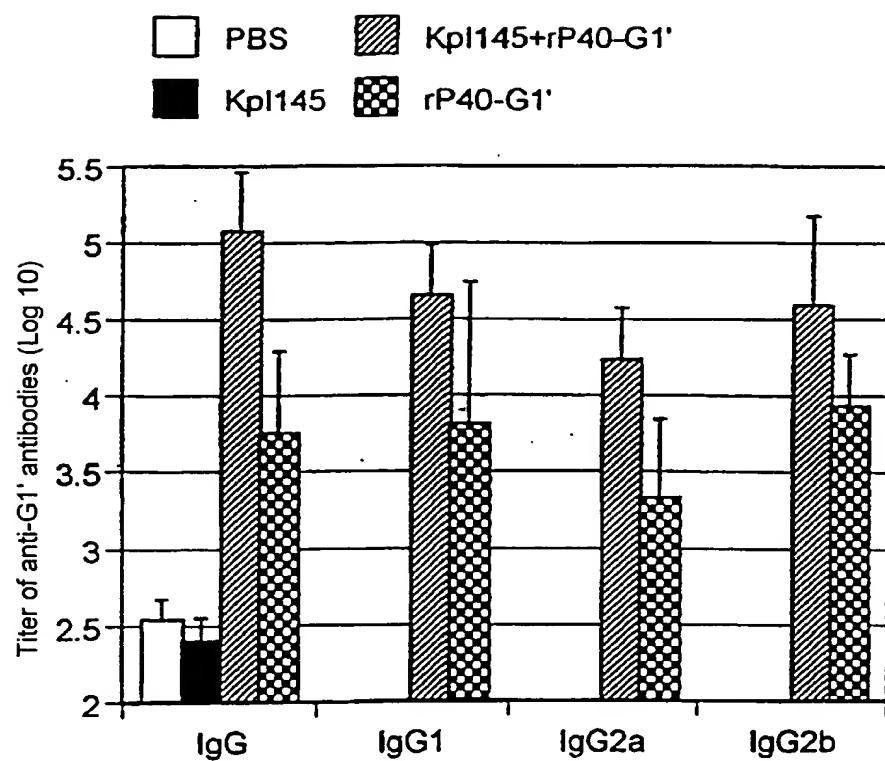


FIG. 7

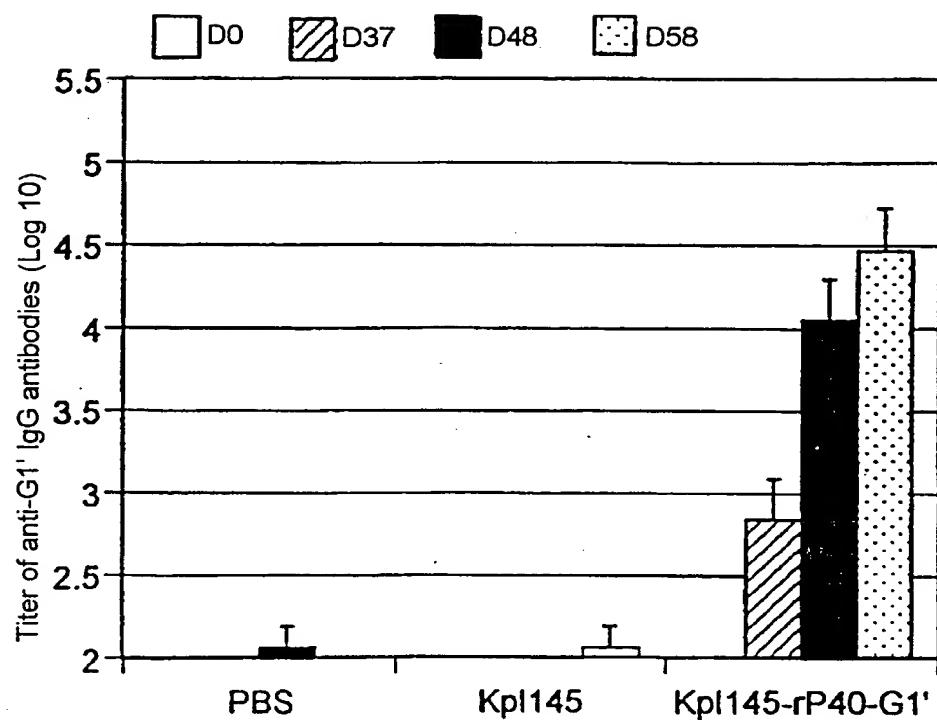


FIG. 8

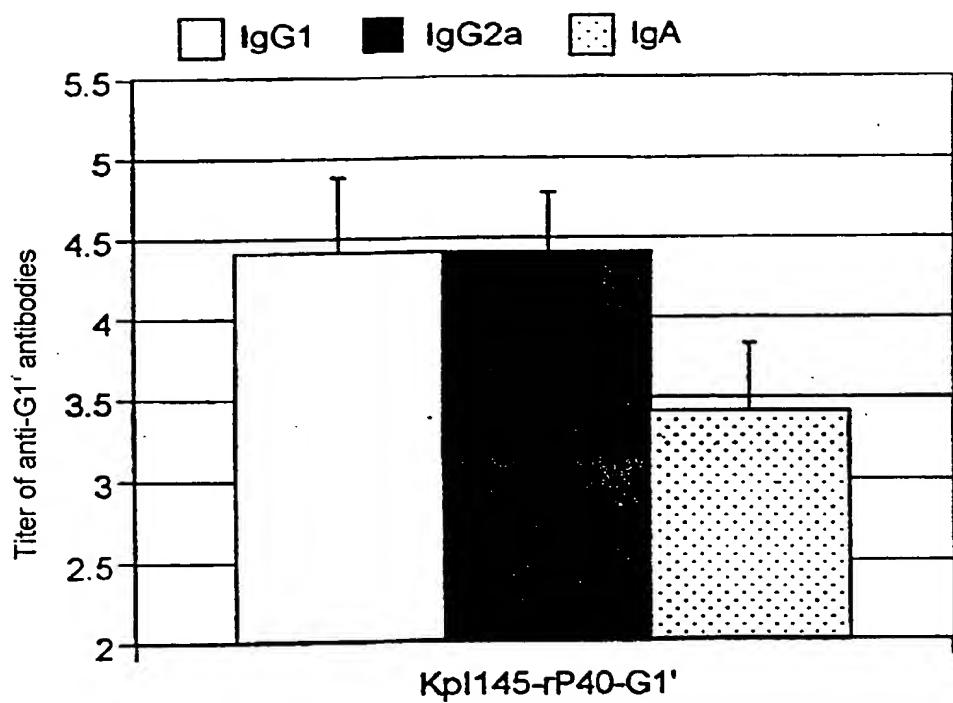


FIG. 9

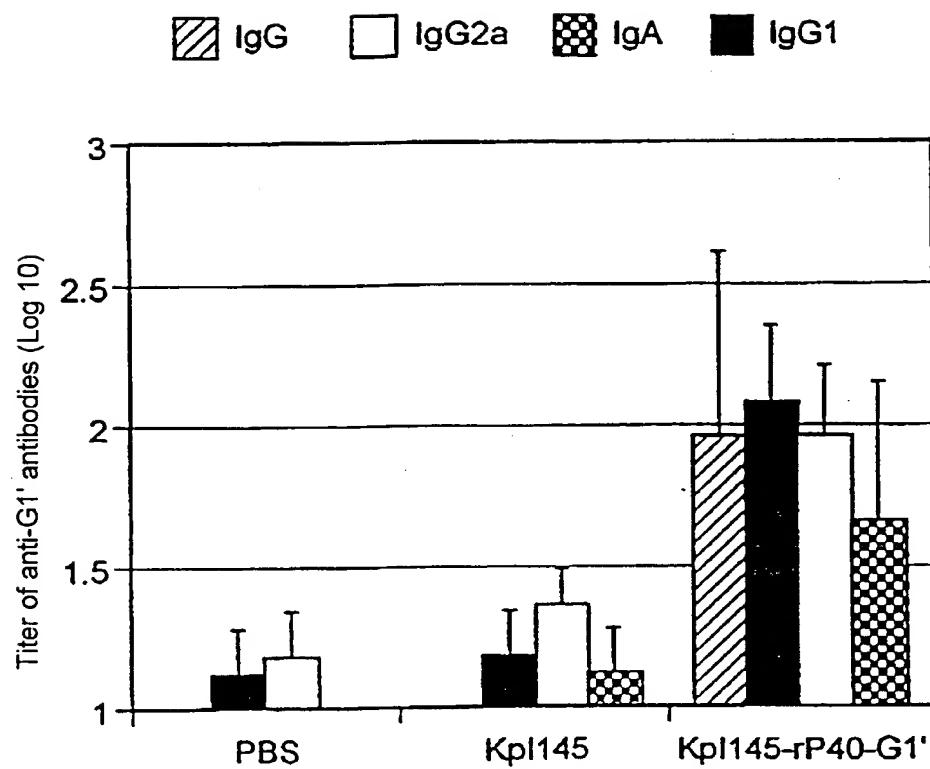


FIG. 10